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THE TREATMENT OF TREE POLLEN SENSITIVITY WITH SINGLE ANNUAL INJECTIONS OF EMULSIFIED EXTRACT. III.

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IN AN ATTEMPT to lessen the time, trouble and expense of treating hay fever caused by sensitivity to tree pollens, 164 allergic patients were given a single injection of emulsified tree pollen extract. The dose varied from 1,700 to 10,000 Protein Nitrogen Units of equal parts of Birch and Oak pollen extracts. The injections were administered between December 10, 1957, and February 5, 1958.

Any patient who reported any symptoms whatsoever during the pollen season was considered to be a failure in treatment. Of these, there were nineteen, whose protocols are given in some detail. The background of these patients and of the 145 others who had no symptoms whatsoever is listed in tabular form.

The first of three papers described a method for avoiding injection reactions.¹ The second described the results of treatment with single annual injections in a series of ragweed pollinosis patients.²

The present or third communication on this subject concerns studies which were originally designed so that no repository injection would be given to any patient unless he could present an authenticated history of at least three consecutive years of tree pollinosis. But, for reasons not germane to this discussion, seven patients with only two consecutive years of symptoms were included and one patient whose classic pollen sensitivity involving eyes, nose and palate had been present for only one pollen season, that of 1956.

The exact duration of symptoms could not be determined in eleven patients in whom the first symptoms were either intermittent or the disorder was for some time not diagnosed correctly. These patients were firm in their conviction that they had been affected for more than ten,

TREE POLLEN SENSITIVITY—BROWN

and probably fewer than fifteen, years. They are listed as having had hay fever for "many" years, and are so accounted for in the 11-20 years group of the first table.

TABLE I. DISTRIBUTION BY YEARS OF SYMPTOMS OF ALLERGIC CORYZA, BRONCHIAL ASTHMA, OR BOTH

1-10	11-20	21-30	31-40	41-50
69	62	22	10	1

Some of the patients who had suffered from pollinosis for three years or more could remember occasional seasons when symptoms were extremely mild. In some whose symptoms dated back more than fifteen years there were those who for reasons of geographical translocation as while in the Armed Services and at sea had periods of no difficulties whatsoever. The disorder, however, returned with exposure to tree pollen in their home environment. Some of the patients who reported having suffered no symptoms may have, therefore, been experiencing a season of spontaneous remission.

With all types of treatment there is the factor of the "placebo reactor." This has been variously estimated to be as high as 30 per cent. We have found this to be true in our own work (unpublished data). But since such "placebo reactors" may report either good results from placebos or poor results from true treatments, they can hardly, to any great extent, vitiate our results.

Of the 164 patients, fifty-three had never previously been treated for sensitivity to tree pollens. The other 111 patients had, in past years, been given conventional treatment with aqueous extracts by others or by us. These "transition patients" had ceased taking their conventional treatment from one to seven months before the repository injection was administered. The second table lists them according to the month in which they ceased injection treatment.

TABLE II. DISTRIBUTION OF TRANSITION PATIENTS ACCORDING TO TIME OF CESSATION OF CONVENTIONAL TREATMENT

Months:	7	6	5	4	3	2	1
Number:	3	2	2	3	12	23	66

The eighty-nine patients who had ceased treatment during the two months before their repository injection were either instructed or preferred to take their routine injections until the date of the new single annual injection could be definitely arranged so that they would not be left

TREE POLLEN SENSITIVITY—BROWN

without protection had there been any change in plans. Some were seen during December and January when they returned for annual re-evaluation study visits. They were told that a single annual injection was available and asked whether they cared to make the transition, in which case the injection was given as part of such studies. Any patient who preferred to continue with traditional methods of treatment was permitted to do so. These patients taking such aqueous injections number in all 554. They serve as controls for the 1,758 patients who so far have had from one to five repository injections for Tree (164), Grass (383), Ragweed pollen (699) and House dust (512).

The delayed action or repository type of injection is not new. Its background and development can only be fully understood, however, in relation to other traditional methods of treatment, especially that using aqueous solutions of pollen.

In 1907, one gram of extracted pollen was arbitrarily postulated as representing 1,000,000 units.³ With no immunochemical basis, 100,000 such Noon-Freeman units were assumed to represent the top dose required for immunity. The interval of one week between injections was convenient but not related to increments in immunity. The spread between the first injection of 40 units and the last of 100,000 units was divided into fifty-four doses to take the patient through the year and into two weeks of the next season. Because there was initially no method of protecting patients against anaphylactoid reactions or of treating them with invariable success should such occur, each patient was actually then, and is now, a subject for exploration. Any injection a patient accepted without local or general reaction was taken to mean that it was safe to give the next larger injection of the series.

With the passage of time some modification of dosage schedules was made. Patients were classified according to sensitivity as related to skin tests into groups AA, A, B, and C. This also was only a practical measure and did not take into consideration the fact that a successfully treated patient, a failure in treatment and a patient never previously treated might all be classified as equally sensitive and placed on the same injection schedule. Also, when a patient placed in any group was successfully taken to the top dose of the series of injections scheduled for that group, it was assumed, for no reason that the patient could be transferred to the next succeeding group and treated with increments of extract in accordance with the arbitrarily selected doses of the new schedule.

When, as a result of treatment based on such a hodge-podge of assumptions, the patient suffered symptoms, it was taken for granted that an insufficient amount of pollen had been injected and greater doses were given for the following year. When the patient did well, the result was ascribed to the treatment and the level of injection dosage reached was considered to be a maintenance dose to be continued indefinitely. On such maintenance dosage injections some patients would, nevertheless, unac-

TREE POLLEN SENSITIVITY—BROWN

countably suffer "good" and "bad" seasons. The good years were ascribed to the treatment and the poor years to exposure of pollen greater than usual. In no other part of the field of internal medicine is a patient treated on the basis of how he says he reacted in the past so as to prevent similar reactions to differing circumstances in the future.

There is absolutely no reason for patients to be treated in this manner unless they wish it so.

In 1923, Sutton⁴ reported on the use of undried, undefatted ragweed pollen suspended in olive oil and given as a single preseasonal injection. Of the patients so treated, 80 per cent reported perfect results and 20 per cent were moderately improved. Not enough immunology was known to enable the physician to determine how much pollen extract to give or when. In conjunction with studies of blocking antibody, Loveless⁵ (over a period of years during which placebo and double blind techniques were employed) ingeniously worked out a correlation between the conjunctival response, the skin test, the time interval and the dose needed for the single visit management of pollinosis. The incidence of reactions (including for statistical purposes all responses, however mild) was approximately 5 per cent, a rate too high for office practice.

In 1940, Freund and McDermott,⁶ however, had successfully demonstrated enhancement of antibody with the use of Freund's Adjuvant, an emulsion of mineral oil. With the use of Atreol (a highly refined mineral oil) and Falba (an emulsifying agent), Loveless was the first to use emulsified extracts in mineral oil in the treatment of pollinosis. Loveless' reaction rate decreased with each successive year. Only two such episodes occurred in 1957, with seventy-three depot or repository injections given to "unprotected" patients (personal communication).

In our office all but two of 1,758 patients have been protected against possible reactions. Seven such reactions have occurred in the group of "protected" patients. One occurred in the present series as urticaria controlled by epinephrine.

At present, each patient is given pseudo-ephedrine (Sudafed, 60 mg, Burroughs Wellcome) or a Luasmin capsule (theophylline sodium acetate 0.2 Gm, ephedrine sulfate 30 mg, and sodium phenobarbital 30 mg, Brewer) by mouth, and an antihistaminic agent, either Chlor-Trimeton (4 mg, Schering) or Theruhistin (4 mg, Ayerst). Other antihistaminic agents have been used with equal success. Epinephrine 1:1000, 0.1 cc is injected proximal to the intended site of the repository injection.

Conjunctival tests are done before "protection" with one drop of non-glycerinated extract and with consecutive concentrations of 10, 20, 40, 80, 160, 320, 640, 1280, 2500, 5000, 7500, 10,000, 15,000 and 20,000 Protein Nitrogen Units/ml. The reaction level is corroborated by the use of the next higher strength instilled into the conjunctival sac of the other eye. Patients suffering from ophthalmic disorders are not

TREE POLLEN SENSITIVITY—BROWN

tested conjunctively, but patients who do not complain of ocular symptoms are tested although we know that the test will not be positive.

The present dosage schedule modified from Loveless is as follows: Patients who suffer from conjunctival symptoms and respond to ophthalmic tests at the 80, 640, 5000 and 10,000 P.N.U./ml. levels respectively receive 2500, 5000, 7500 and 10,000 P.N.U. in a single injection. In our first studies with tree pollens I was more cautious and the respective doses were 1700, 3300 and 5000 P.N.U. Only one patient was given 10,000 P.N.U.

TABLE III. DISTRIBUTION BY AGE AND SEX

	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80
Females	4	18	14	11	15	7	1	0
Males	18	28	17	14	9	4	3	1
Totals	22	46	31	25	24	11	4	1

TABLE IV. DISTRIBUTION BY EMULSION DOSAGE

Protein Nitrogen Units	1700	2500	3300	4000	5000	7500	10,000
Number of Patients	37	2	67	1	54	2	1

At present, patients who do not respond ophthalmically but show positive skin tests by the pressure puncture method using glycerinated extracts of the strength of 7000 P.N.U./ml are given a single emulsion injection of 2500 P.N.U. A patient with a positive intracutaneous test at or above ten, but below the level of 1000 P.N.U./ml, is given 5000 P.N.U. A reaction at the 1000 P.N.U./ml level is taken to mean that the patient needs 7500 P.N.U., and a positive test to 2000 P.N.U./ml indicates a single total dose injection of 10,000 P.N.U. We do not go above 2000 P.N.U./ml for skin testing solutions nor have we so far gone above 10,000 P.N.U. for a single emulsion injection.

The prescribed amount of extract is emulsified with Falba and Atreol and injected either in one dose or using the same needle channel in two to five portions separated by intervals of ten to twenty minutes. Fifteen minutes following the pollen emulsion injection, delayed-action epinephrine (Sus-Phrine, Brewer) is injected in a dose of 0.1 cc into the outer aspect of the upper third of the other arm.

Forty-six patients suffered from pollen asthma alone and forty-one from hay fever (allergic coryza) alone, and eighty-seven from both.

The third table lists the distribution of patients by age and sex.

The fourth table shows the number of patients who received each of the doses administered in a single injection. Of the 164 patients, 122 required either 3300, 4000 or 5000 P.N.U. Thirty-seven were given as little as 1700 P.N.U.

TREE POLLEN SENSITIVITY—BROWN

TABLE V. PATIENTS WITH NO PREVIOUS TREATMENT

No.	Patient	Sex	Age	Diagnosis	Years	Tests P.N.U./cc			Emulsion Total P.N.U.	Date Given
						I.C.	PP	Ophth.		
1	LA	M	27	BA	17	2000		10,000	1700	12/11/57
2	AB*	F	30	AC	4	2000		1,000	3300	12/17/57
3	LB	M	18	BA	13	1000		625	5000	1/22/58
4	FB	M	21	BA	20	2000		10,000—	3300	12/18/57
5	GB	M	40	AC	8			10,240—	5000	2/ 5/58
6	RC	M	22	AC & BA	12			625	5000	1/14/58
7	JC	M	14	BA	6	2000		10,000	3300	12/31/57
8	DC	F	38	AC & BA	18	2000		10,000—	5000	1/ 8/58
9	SD	M	8	AC & BA	3	2000		10,000—	3300	12/17/57
10	PD	M	36	BA	34		+	1,250	3300	12/26/57
11	LD*	F	25	AC & BA	7		+	50	3300	12/18/57
12	AD	F	49	AC & BA	35		+	39	2500	1/30/58
13	FD*	M	49	AC	31		+	39	2500	1/30/58
14	BE	F	25	AC & BA	24	1000		625	5000	1/ 8/58
15	JF	M	47	AC & BA	"many"		+	625	5000	1/21/58
16	JF	M	8	AC & BA	2	2000		1,250	5000	2/ 6/58
17	HG	F	9	BA	4	2000		10,000	5000	1/14/58
18	SH	F	16	AC	5	2000		625	3300	12/30/57
19	CH*	F	20	AC	5	2000		250	3300	12/17/57
20	EH	F	41	BA	9	2000		2,500	5000	2/ 4/58
21	SK	F	10	AC	5	2000		10,000	7500	12/31/57
22	RK	M	10	BA	8		+	156	3300	12/23/57
23	CL	M	29	BA	"many"	2000—		10,000—	1700	12/ 9/57
24	NL	F	28	BA	8	2000		10,000—	5000	1/15/58
25	IL	M	21	AC	18	2000		Not Done	1700	12/11/57
26	TL*	F	33	AC & BA	20	2000		10,000—	3300	12/18/57
27	FM	M	22	AC	6	2000		10,000	3300	12/30/57
28	MM	M	25	BA	24	2000		5,000—	1700	12/11/57
29	CM	F	29	BA	19	2000		100	1700	12/ 9/57
30	FM	M	78	AC	30	2000		10,000—	3300	12/19/57
31	RN*	M	6	AC & BA	2		+	39	3500	1/ 7/58
32	CO	M	42	AC	1	100		250	5000	1/ 2/58
33	RP*	M	13	AC	4	2000		500	3300	12/16/57
34	AP	M	15	AC	3	100		250	1700	12/12/57
35	JR	M	5	BA	4	2000		10,000—	3300	12/17/57
36	MR	F	44	AC	29	2000		1,000	1700	12/10/57
37	PR	M	8	BA	6	2000		10,000—	1700	12/ 9/57
38	JS	F	22	AC	17	2000		10,000—	3300	12/24/57
39	JS	F	8	BA	2	2000		2,500	5000	1/21/58
40	JS	F	15	AC & BA	12	1000		1,250	5000	1/21/58
41	HS	M	61	BA	24	2000		10,000—	3300	12/24/57
42	MS	M	9	AC	3	2000		10,000—	1700	12/12/57
43	CS	M	48	AC	19	2000		10,000	5000	1/30/58
44	ES	M	15	AC	10	2000		10,000—	3300	12/23/57
45	NS	F	26	BA	25	1000		10,000—	3300	12/17/57
46	PS	F	33	AC & BA	23	2000		1,000	1700	12/10/57
47	DS	F	17	AC	16	2000		2,500	5000	1/ 7/58
48	AT	M	18	BA	2	2000		10,000	3300	12/26/57
49	DW	M	15	AC & BA	14		+	500	3300	12/18/57
50	JW	M	29	AC	17	1000		78	5000	1/ 8/58
51	CW	M	28	AC	"many"	2000		10,000—	5000	1/21/58
52	HW*	M	36	AC & BA	16	2000		50	1700	12/12/57
53	MW	F	42	AC	16		+	156	3300	12/26/57

*Patients who reported symptoms.

The fifth table lists the patients who had never previously received injection treatment. They are identified by number and first and last initials, and by sex and age. The asterisks draw attention to the patients who reported symptoms. The diagnosis is noted as AC for Allergic Coryza and BA for Bronchial Asthma. The next column lists the years of the duration of the disorder. The seventh column gives the strength of the pollen extract as an intracutaneous test which elicits a positive reaction. The eighth column notes the presence of a pressure puncture or scratch test in which case intracutaneous tests were not done. The ninth column gives the strength of the solution of which one drop instilled into the conjunctival sac causes a positive reaction. The minus sign following the strength in units signifies the absence of a response

TREE POLLEN SENSITIVITY—BROWN

at that level, an expected finding in patients who do not respond to pollen ophthalmically. The last two columns list the total dose injected and the date it was given.

The sixth table is similarly arranged except that the patients, all of whom had received aqueous injection treatment, are grouped by the month when aqueous injection extract was last used. Again asterisks label those who reported symptoms. It will be noted that six of sixty-six who made the transition within one month and eight of fifty-three who had never had treatment were listed as failures. The difference is too slight to be statistically significant.

Further details of the patients who failed to respond to treatment are given in their protocols. For the record, any symptoms whatsoever, and however mild, suffered during the Birch and Oak pollen seasons are listed.

The following protocols include this information: the patient's name (two initials); sex (as M or F); age; diagnosis (as AC, allergic coryza or BA, bronchial asthma or both); duration of symptoms in years; diagnosis of types of pollinosis; previous aqueous treatment, if any (as Prev. Rx with dosage in Protein Nitrogen Units and date of cessation); the level of positive response to intracutaneous tests (as IC + # P.N.U./ml) or pressure puncture positive (as PPP); the level of response (— indicates Negative) to ophthalmic tests (as Ophth. # P.N.U./ml); total of the tree emulsion injection (as P.N.U.) and date given; total dosage of the grass emulsion injection, if any; the onset of symptoms and possible reasons for the failure of repository treatment.

1. RB, M, 16. AC, 6. Tree, Grass and Ragweed pollinosis. Prev. Rx, 4500 P.N.U., one month before emulsion injection; IC + 2000 P.N.U./ml; Ophth. + 5000 P.N.U./ml; Tree Repository injection 3300 P.N.U., 12-30-57. Nasal stenosis began 6-4-58 with the overlapping of Tree and Grass pollination periods. It lasted seven days and was relieved by Perazil (50 mg, Burroughs Wellcome) and Diafen (2 mg, Schenlabs).

? Overlapping pollen seasons. ?? Low dose injected.

2. TM, M, 13. AC & BA for "many years." Tree, Grass and Ragweed pollinosis. Prev. Rx, 3500 P.N.U., one month before emulsion injection. IC + 2000 P.N.U./ml; Ophth. + 5000 P.N.U./ml. Tree Repository injection, 3300 P.N.U., 12-23-57. Grass Repository injection, 7500 P.N.U., 2-20-58. Nasal stenosis began the last two weeks of May. A cough and wheeze began the first week of June during the overlapping of Tree and Grass pollination periods. No symptoms subsequently.

? Overlapping pollen seasons. ?? Low dose injected.

3. AB, F, 30. AC, 4. Tree, Grass and Ragweed pollinosis. No previous treatment. IC + 2000 P.N.U./ml; Ophth. + 1000 P.N.U./ml. Tree Repository injection, 3300 P.N.U., 12-17-57. Grass Repository injection, 3000 P.N.U., 2-25-58. Mild symptoms began during the last days of May with the overlapping of Tree and Grass pollen seasons. Relieved by Chlor-Trimeton (4 mg, Schering). Symptoms recurred on 6-8-58 and lasted until 6-25-58.

? Overlapping pollen seasons. ?? Low dose injected. ??? Gross pollen symptoms.

TREE POLLEN SENSITIVITY—BROWN

TABLE VI. TRANSITION PATIENTS

7 Month Transition Patients											
No.	Patient	Sex	Age	Diagnosis	Years	Aqueous P.N.U.	P.N.U./cc			Emulsion	Date Given
							I.C.	PP	Ophth.		
1	AC	F	23	BA	22	400	+ 100		1,250	4000	1/14/58
2	CD*	F	34	AC	9	3000	+2000		10,000—	5000	1/ 2/58
3	BM	F	43	AC	19	1000	+1000		10,000—	5000	1/ 2/58
6 Month Transition Patients											
1	RL	M	19	BA	12	3000	+2000		10,000—	3300	12/30/57
2	AO	M	53	AC	34	300	+2000		1,000	1700	12/10/57
5 Month Transition Patients											
1	EC	F	17	AC	6	2800	+ 100		5,000	1700	12/11/57
2	GL	M	53	AC	30	4500	+2000		1,250	5000	1/21/58
4 Month Transition Patients											
1	DC	M	13	AC & BA	7	3300	+2000		160	1700	12/12/57
2	RJ	M	33	AC	15	150	+2000		1,000	1700	12/ 9/57
3	MM	F	54	AC & BA	44	1400	+ 100		100	1700	12/10/57
3 Month Transition Patients											
1	OB	F	31	BA	6	3000	+2000		10,000—	5000	2/ 4/58
2	MG*	M	43	BA	8	3000	+2000		5,000	3300	12/30/57
3	LG*	F	16	AC	3	250	+2000		500	3300	12/18/57
4	JJ	M	7	AC & BA	5	3500	+2000		Not Done	3300	12/30/57
5	SL*	M	39	AC	17	800	+2000		500	1700	12/11/57
6	RP	M	41	AC	"many"	2600	+2000		10,000—	1700	12/12/57
7	AS	F	48	AC & BA	16	2000	+1000		1,280	5000	2/ 4/58
8	BS	F	62	AC & BA	19	800	+1000		5,000	3300	12/19/57
9	GS	M	64	AC	30	2600	+2000		625	5000	1/ 7/58
10	ES	F	36	AC & BA	7	4000	+2000		10,000—	3300	12/26/57
11	RZ	M	8	AC & BA	7	1700	+1000		10,000—	5000	1/ 8/58
12	MT	F	43	AC & BA	10	1400	+2000		5,000	5000	1/21/58
2 Month Transition Patients											
1	AA	M	58	BA	14	3300	+2000		10,000—	1700	12/ 9/57
2	DA	M	32	BA	4	5000	+2000		10,000—	1700	12/10/57
3	GB	M	16	BA	4	4000	+2000		10,000—	3300	12/19/57
4	OC	F	39	BA	11	4500	+2000		10,000—	1700	12/12/57
5	JD	F	54	AC	"many"	2800	+2000		10,000—	3300	12/16/57
6	RD	M	11	AC	6	3000	+2000		625	5000	1/21/58
7	WD	M	21	AC	7	9000	+2000		10,000—	3300	12/23/57
8	DD	M	9	BA	6	4000	+2000		10,000—	1700	12/10/57
9	CF	F	23	BA	15	5000	+2000		10,000—	3300	12/30/57
10	BC	F	32	BA	11	5000	+2000		10,000—	1700	12/12/57
11	DG	F	58	BA	14	4000	+1000		Not Done	3300	12/19/57
12	BH	M	17	BA	13	2600	+2000		10,000	3300	12/19/57
13	AH	F	53	BA	3	5000	+2000		10,000—	3300	12/19/57
14	DK	F	48	BA	29	4500	+2000		10,000—	1700	12/11/57
15	MP*	M	29	AC	"many"	800	+2000	+	625	5000	1/ 7/58
16	EP	F	47	AC & BA	3	3000	+2000		5,000	3300	12/26/57
17	JR	M	37	BA	28	1000	+2000		10,000—	5000	1/ 7/58
18	CS	F	45	AC & BA	22	4500	+2000		10,000—	5000	1/15/58
19	WM	F	14	BA	10	3500	+2000		10,000—	5000	1/ 9/58
20	WS	M	37	AC	"many"	5500	+2000	+	Not Done	5000	1/21/58
21	JS	F	50	BA	33	3500	+2000		5,000	3300	12/26/57
22	DS	M	18	AC	11	2100	+2000		625	5000	1/22/58
23	GZ	F	35	AC	20	600	+2000		1,250	5000	1/ 8/58

(Although the patient reported great improvement, the presence of sneezing requiring medication labels the result as a failure.)

4. RG, M, 18. AC, 4. Tree, Grass and Ragweed pollinosis. Prev. Rx, 5000 P.N.U., one month before emulsion injection. IC + 1000 P.N.U./ml; Ophth. + 2000 P.N.U./ml. Tree Repository injection, 3300 P.N.U., 12-19-57. Grass Repository injection, 5000 P.N.U., 3-4-58. Reported 6-16-58 that with applications of Colgate Cosmétique, sneezing occurred during late May and early June, lasting one week. No other symptoms except some sneezing in an air-conditioned department store.

TREE POLLEN SENSITIVITY—BROWN

TABLE VI. TRANSITION PATIENTS — CONTINUED

1 Month Transition Patients											
No.	Patient	Sex	Age	Diagnosis	Years	Aqueous P.N.U.	P.N.U./cc			Emulsion	Date Given
							I.C.	PP	Ophth.		
1	DA	M	19	BA	17	6000	+2000		10,000—	3300	12/17/57
2	VA	F	18	BA	12	5500	+2000		10,240	3300	12/18/57
3	NA	M	11	BA	10	500	+2000		10,000	3300	12/26/57
4	JB	F	19	BA	18	1600	+2000		10,000—	5000	1/ 2/58
5	JB	F	20	AC	19	1600	+2000		10,240—	5000	1/ 2/58
6	SB	M	10	AC & BA	4	2600	+2000		10,240—	3300	12/17/57
7	RB*	M	16	AC	6	4500	+2000		5,000	3300	12/30/57
8	JB	F	18	AC & BA	5	4000	+2000		10,000	5000	1/ 7/58
9	LB	F	8	BA	6	700	+2000		10,000	1700	12/10/57
10	SB	M	31	AC	15	300	+1000		10,000—	3300	12/19/57
11	RB	M	15	AC & BA	5	4000	+1000		312	7500	12/31/57
12	BB	F	20	AC	8	4500	+1000		10,000—	3300	12/31/57
13	ZC	M	21	AC	20	2500	+2000		10,000—	5000	1/ 2/58
14	NC	F	11	BA	3	1600	+2000		10,000	5000	1/14/58
15	FC	M	4	AC & BA	3	160	+2000		Not Done	1700	12/10/57
16	GC	M	36	AC	20	160	+2000		1,000	1700	12/10/57
17	PC	M	12	AC & BA	11	2500	+ 100		312	3300	12/23/57
18	FD	M	36	BA	26	1600	+2000		10,000—	5000	1/ 7/58
19	ED*	F	27	AC	9	3500	+2000		10,000—	3300	12/26/57
20	JD	M	52	AC & BA	20	800	+2000		50	1700	12/ 9/57
21	RD	M	34	AC	2	6000	+1000		1,250	5000	1/ 9/58
22	AD	F	18	AC & BA	17	1000	+2000		10,000—	3300	12/17/57
23	JE	M	15	BA	12	1300		+	10,000	3300	12/23/57
24	RF	M	8	BA	4	7500	+2000		10,000—	5000	1/15/58
25	RG	M	25	AC	2	250	+2000		10,240—	1700	12/11/57
26	SG	M	9	BA	8	2000	+2000		10,000—	1700	12/10/57
27	RG*	M	18	AC	4	5000	+1000		2,500	3300	12/19/57
28	WH	M	61	BA	15	5000	+2000		10,000—	1700	12/10/57
29	EH	F	43	AC & BA	22	3500	+2000		10,000—	5000	1/ 2/58
30	PH	M	45	AC	2	2500	+ 100		250	3300	12/19/57
31	MH*	F	14	BA	7	2500	+2000		5,000	1700	12/ 9/57
32	MH	F	28	BA	"many"	250	+2000		2,500	3300	12/17/57
33	EK	F	42	BA	16	4000	+2000		10,000—	1700	12/11/57
34	SK	M	28	BA	22	250	+2000		250	1700	12/12/57
35	ML	F	11	BA	5	400	+2000		5,000	5000	1/ 7/58
36	EL	M	20	AC & BA	17	4500	+1000		10,000—	5000	1/ 2/58
37	ML	F	48	AC	24	3000	+2000		10,000	3300	12/17/57
38	CM	F	38	AC	"many"	800	+1000		10,000	3300	12/19/57
39	RM	M	18	BA	12	1000	+2000		10,000—	5000	1/ 8/58
40	EM	M	30	BA	29	3500	+2000		10,000—	3300	12/17/57
41	WM	M	9	AC	5	700		+	250	3300	1/ 2/58
42	MM	M	39	BA	34	5000	+2000		10,000	1700	12/12/57
43	RM	M	15	AC & BA	7	3500	+2000		10,000—	3300	12/19/57
44	JM	M	9	AC & BA	8	700	+2000		10,000—	5000	1/ 9/58
45	TM*	M	13	AC & BA	"many"	3500	+2000		5,000	3300	12/23/57
46	JM	M	47	AC	35	4000	+2000		2,500	3300	12/26/57
47	EO	M	29	AC & BA	27	250		+	39	3300	12/26/57
48	NP	F	24	AC	23	3500	+2000		10,000—	5000	1/ 2/58
49	SP	F	24	BA	17	600	+ 100		5,000	1700	12/12/57
50	TP	F	39	AC & BA	29	420		+	500	3300	12/18/57
51	BP	F	13	BA	12	900	+ 100		5,000—	5000	1/ 7/58
52	RR	M	11	BA	6	1600	+2000		10,000—	5000	1/15/58
53	RR	M	33	AC & BA	32	3100	+2000		250	1'00	12/ 9/57
54	AR	F	56	BA	16	3500	+2000		10,000—	10000	1/16/58
55	RS	M	23	BA	21	3000		+	2,500	1'000	1/15/58
56	PS	M	13	BA	6	160	+ 100		10,000—	3300	12/30/57
57	JS	M	10	AC	7	300	+2000		10,000—	3500	12/31/57
58	DS	F	12	AC	11	700	+2000		2,500	5000	1/22/58
59	ES	F	23	AC	10	2000	+2000		Not Done	3'00	12/23/57
60	ES	F	55	AC & BA	"many"	200	+1000		625	3'00	12/30/57
61	TS*	M	16	BA	15	2500	+2000		10,000	3300	12/31/57
62	HW	M	43	AC & BA	33	3500	+2000		10,000—	3'00	12/19/57
63	MW	F	58	AC & BA	11	3000	+2000		5,000	1'000	1/ 7/58
64	MW	F	11	BA	9	350	+ 100		675	1'000	1/21/58
65	SZ	M	12	AC & BA	2	1300	+ 100		5,000	3'00	12/26/58
66	MH	F	45	BA	35	3600	+2000		10,000—	3300	12/18/57

? Overlapping pollen seasons. ?? Insufficient protection by low dose injected.
 ??? Cosmetic sensitivity.

5. FD, M, 49. AC, 31. Tree, Grass and Ragweed pollinosis. No previous treatment; PPP; Ophth. + 39 P.N.U./ml; Tree Repository injection, 2500 P.N.U.,

TREE POLLEN SENSITIVITY—BROWN

1-30-58; Grass Repository injection, 5000 P.N.U., 2-18-58. "Sniffles" began 5-1-58, being intermittently present for one week, usually on arising. Relieved by Chlor-Trimeton (4 mg, Schering).

? Extremely sensitive patient. ?? Low dosage.

6. CH, F, 20. AC, 5. Tree and Ragweed pollinosis. No previous treatment. IC + 2000 P.N.U./ml; Ophth. + 250 P.N.U.; Tree Repository injection, 3300 P.N.U., 12-17-57. No Grass Repository injection given. Skin test sensitive but not previously clinically sensitive to grass pollens. Nasal stenosis, sneezing and itching of the palate began the first week of June.

? Overlapping pollen seasons. ?? Untreated grass pollinosis.

7. LG, F, 16. AC, 3. Tree, Grass and Ragweed pollinosis. Prev. Rx, 250 P.N.U., three months before emulsion injection. IC + 2000 P.N.U./ml; Ophth. + 500 P.N.U./ml; Tree Repository injection, 3300 P.N.U., 12-18-57. Grass Repository injection, 7500 P.N.U., 2-19-58. Nasal stenosis and postnasal drip began 5-3-58. Relieved by Phenergan (25 mg, Wyeth). No Grass pollen symptoms.

? Extreme sensitivity. ?? Insufficient protection by low dose injection.

8. RP, M, 13. AC, 4. Tree, Grass and Ragweed pollinosis. No previous treatment. IC + 2000 P.N.U./ml; Ophth. + 500 P.N.U./ml; Tree Repository injection, 3300 P.N.U., 12-16-57. Grass Repository injection, 5000 P.N.U., 2-21-58. Ocular and nasal symptoms began 5-1-58 and occurred almost every day, lasting in all for two weeks. No medication was required and the symptoms had not recurred as of 6-4-58 and 7-31-58.

? Sensitivity. ?? Insufficient immunity.

9. ED, F, 27. AC, 9. Tree, Grass and Ragweed pollinosis. Prev. Rx, 3500 P.N.U., one month before emulsion injection. IC + 2000 P.N.U./ml; Ophth. —10,000 P.N.U./ml (no ocular symptoms); Tree Repository injection, 3300 P.N.U., 12-26-57. Symptoms began during the first week of April and lasted for seven days.

? Symptoms not due to Tree pollen during the week of rainy weather. ?? U.R.T. infection.

10. CD, F, 34. AC, 9. Tree and Ragweed pollinosis. Prev. Rx, 3000 P.N.U., seven months before emulsion injection; IC + 2000 P.N.U./ml; Ophth. —10,000 P.N.U./ml (no ocular symptoms); Tree Repository injection, 5,000 P.N.U., 1-2-58. Two days of typical hay fever during mid-May; no medication required.

? Tree pollen. ?? Other exposure.

11. LD, F, 25. AC, 7. Tree, Grass and Ragweed pollinosis. No previous treatment. PPP; Ophth. + 50 P.N.U./ml; Tree Repository injection, 3300 P.N.U., 12-18-57. Reported symptoms of nasal stenosis, epiphora, cough and wheeze while en route from Boston to New York by car on 5-3-58, while in New York on 5-4-58, and during return, 5-6-58. No symptoms since.

? Insufficient protection. ?? Overwhelming exposure to pollen or combined exposure to pollen and house dust.

12. MH, F, 14. BA, 7. Tree and Ragweed pollinosis. PPP to grass pollens but no clinical symptoms or physical findings. Prev. Rx, 2500 P.N.U., with one aqueous injection being taken in error on 1-18-58, although the Tree Repository injection, 1700 P.N.U., was given on 12-9-57. IC + 2000 P.N.U./ml; Ophth. +

TREE POLLEN SENSITIVITY—BROWN

5000 P.N.U./ml. Reported two days of epiphora and conjunctival inflammation 5-20-58 and 5-21-58. No medication required, and no symptoms since.

? Peak of Tree pollen season. ?? Insufficient protection.

13. TL, F, 33. AC & BA, 20. Tree, Grass and Ragweed pollinosis. No previous treatment. IC + 2000 P.N.U./ml; Ophth. —10,000 P.N.U./ml (no ocular symptoms). Tree Repository injection, 3300 P.N.U., 12-18-57. Grass Repository injection, 7500 P.N.U., 2-17-58. Reported 5-28-58 having some symptoms during the first two weeks of May. Relieved by Hydrillin (25 mg, Searle), one daily being sufficient.

? Insufficient protection.

14. RN, M, 6. AC & BA, 2. Tree and Grass pollinosis. IC + 100 P.N.U./ml; Ophth. + 250 P.N.U./ml. Tree Repository injection, 3500 P.N.U., 1-2-58. Grass Repository injection, 3000 P.N.U., 3-6-58. Suffered a systemic reaction with generalized urticaria and bronchospasm. Relieved by epinephrine 1:1000, 0.2 cc, s.c., and ephedrine, 60 mg p.o. No recurrence. Symptoms occurred during the last week of May as nasal stenosis. Relieved by Chlor-Trimeton (4 mg, Schering). Brief, mild bronchospasm occurred but required no treatment. No symptoms since.

? Overlapping Tree and Grass pollen seasons.

15. MP, M, 29. AC, "many years." Tree, Grass and Ragweed pollinosis. Prev. Rx, 800 P.N.U., two months before emulsion injection. PPP; Ophth. + 625 P.N.U./ml; Tree Repository injection, 5000 P.N.U., 1-7-58. Nasal symptoms consisting of two sneezes each morning for one week during the second week of May. No other symptoms and no difficulties since.

(This patient is included with the group of "failures" so that all symptoms, however mild, may be ascribed to insufficient protection.)

16. AS, F, 48. AC & BA, 16. Tree and Ragweed pollinosis. Large reactions to Grass pollen tests but no previous clinical symptoms. Prev. Rx, 2000 P.N.U., three months before emulsion injection. IC + 2000 P.N.U./ml; Ophth. + 1280 P.N.U./ml; Tree Repository injection, 5000 P.N.U., 2-4-58. Nasal stenosis and coryza began 5-22-58, and gradually diminished by the first week in June. Relieved by Perazil (50 mg, Burroughs Wellcome) taken each morning.

? Overlapping Tree and Grass pollen seasons. ?? Insufficient protection for Tree pollen sensitivity. ??? Developing clinical sensitivity to Grass pollen.

17. TS, M, 16. BA 15. Tree, Grass and Ragweed pollinosis. Prev. Rx, 2500 P.N.U., one month before emulsion injection. IC + 2000 P.N.U./ml; Ophth. —10,000 P.N.U./ml (no ocular symptoms). Tree Repository injection, 3300 P.N.U., 12-31-57. Grass Repository injection, 5000 P.N.U., 2-24-58. Mild asthma requiring no medication on June 2, 3, and 4, 1958, relieved by Hydrillin (25 mg, Searle).

? Overlapping Tree and Grass pollen seasons. ?? Insufficient protection.

18. HW, M, 36. AC & BA, 16. Tree and Grass pollinosis. No previous treatment. IC + 2000 P.N.U./ml; Ophth. + 50 P.N.U./ml. Tree Repository injection, 1700 P.N.U., 12-12-57. Grass Repository injection, 5000 P.N.U., 2-27-58. Symptoms began 5-18-58 as cough and phlegm occurring from 8:00 to 10:00 A.M. for five days (no ocular or nasal symptoms or bronchospasm). Relieved by Sudafed (60 mg, Burroughs Wellcome) taken on arising.

? Insufficient protection.

TREE POLLEN SENSITIVITY—BROWN

19. MG, M, 43. BA, 8. Tree, Grass and Ragweed pollinosis. Prev. Rx, 2500 P.N.U. three months before emulsion injection. IC + 2000 P.N.U./ml; Ophth. + 5000 P.N.U./ml. Tree Repository injection, 3300 P.N.U., 12-30-57. Grass Repository injection, 7500 P.N.U., 3-20-58. Symptoms 4-15-58 to 4-25-58, ophthalmic and nasal. Assistant ill, daughter in hospital. Patient, a florist, exposed to fresh flowers twelve to fourteen hours daily.

? Insufficient treatment. ?? Other factors. (As of 7-1-58, no further difficulty after 4-25-58).

One factor is immediately obvious. Fifteen of the nineteen patients are sensitive to both tree and grass pollens. Three more (the sixth, twelfth and sixteenth) had reacted by test to grass pollen but had presented no history of grass pollinosis. Only one (the tenth) presents neither a history of grass pollen sensitivity nor positive skin tests to grass pollen. She reported only two days of symptoms during mid-May. She and eight others (the seventh, eighth, ninth, eleventh, thirteenth, fifteenth, sixteenth and eighteenth) reported symptoms during the tree pollen season although one (the ninth) had one week of hay fever in early April. All the others had difficulty when the overlapping of the tree and grass seasons occurred, their symptoms ceasing when the tree pollen was no longer prevalent although grass pollen was in the air. Their repository injections of grass pollen extract protected them against the grass pollen, in that by July 31, 1958, no further symptoms had been reported.

The results speak for themselves. In all, 164 tree pollen sensitive patients were treated with a single annual emulsion injection of tree pollen extract. All nasal or bronchial difficulties of any type, mild or severe, or suffered under any circumstances, were labeled as failures in treatment. Of fifty-three patients who had previously responded to tree pollen with either bronchial asthma or allergic coryza or both, but who had never before been treated, eight reported some symptoms. Of another series of 111 patients, who had previously been treated with multiple injections of aqueous extract, but who had ceased treatment one to seven months before being given their repository injection, eleven reported having had symptoms. Of those who did report having hay fever it occurred in nine of the nineteen during the overlapping of the tree and grass pollen seasons. These patients were sensitive clinically or by skin test to both pollens. Their symptoms ceased when they were no longer exposed to tree pollens. In ten others of the 164 patients treated, symptoms only occurred during the tree pollen season. No explanation is offered for this high percentage of failure excepting perhaps that too low a dose of pollen extract was injected. This will be corrected for the tree pollen season of 1959, for the reason that treatment of hay fever due to tree pollen sensitivity should, on the basis of present knowledge, result in more than 95 per cent of the patients reporting perfect results.

TREE POLLEN SENSITIVITY—BROWN

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THE SCIENTIST AND HISTORY

"The scientist, then, can never relax in his efforts and enjoy himself, like a genial and sensible grammarian, but must be prepared to learn new things every day, and, what is worse, unlearn others with which he has grown intimate, and change the tenets of a lifetime on fundamental points. No wonder that such a harassed individual is generally unwilling to contemplate the past, or, should he have any velleities to do so, unable to do it well. He innocently believes, it may be, that he knows how to do it. Historical work, he seems to think, consists in taking a few old books and copying from them this and that. He may be well trained and fastidious in his own exacting technique, yet not realize that the technique of establishing the truth, or the maximum probability, of past events has its own complicated rules and methods. Historical work, as he conceives it in his candor, is exceedingly easy; almost all that is needed, he thinks, is to know how to read and write, and he despises it accordingly. He does not realize that he is merely despising his perverted image of it. The historian whom he scorns and ridicules is nobody but himself."—GEORGE SARTON, *The Study of the History of Science*, New York, Dover Publications, Inc., copyrighted, 1936.

VITAMIN A ABSORPTION IN ALLERGIC ENTERITIS IN INFANTS AND CHILDREN

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THAT ALLERGY to foods may cause various clinical symptoms such as nausea, emesis, colic, abdominal distention, mucous diarrhea and occasionally interference with normal growth patterns in infants and children has been known for years to practicing pediatricians¹⁻⁶ and academic investigators⁷⁻¹⁰ alike. In recent years some authors¹¹⁻¹⁴ noting the similarity of the symptoms of some of these children to "idiopathic celiac disease," have suggested the term "allergic celiac syndrome" to describe their condition.

The stimulus for this study was the chance observation of an allergic infant whose "celiac symptoms" were so marked that they suggested the diagnosis of cystic fibrosis of the pancreas. The purpose of the study was (1) to investigate the frequency of allergic steatorrhea in hospitalized pediatric patients, (2) to study fat absorption in these infants by differential absorption of fat-soluble and water-soluble forms of vitamin A, and (3) to re-evaluate the diagnostic criteria of the "allergic celiac syndrome." In a previous communication¹⁵ two infants whose symptoms seemed to meet these criteria were described in detail.

METHODS

In an attempt to find some subjects with allergic steatorrhea, a case-finding program was begun at the Strong Memorial Hospital in the Fall of 1952. The authors were alerted by the Director of the Pediatric Chemistry Laboratory when either the outpatient department or the inpatient service sent requests for the following determinations: fecal fat content, duodenal juice enzyme assay, and serum Vitamin A concentration. In addition, members of the house staff were asked to report patients whose symptoms or history suggested the diagnosis of gastrointestinal allergy. In each case the history was carefully reviewed for indications of allergy in the patient's history or in that of the siblings and parents. A careful physical examination was made to find other possible allergic disorders such as allergic rhinitis, atopic dermatitis, or asthma.

Where feasible, the following laboratory data were obtained on each child:

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ALLERGIC ENTERITIS—JOHNSTONE AND McCOORD

TABLE I. EFFECT OF ADMINISTRATION OF THE OILY AND WATER-SOLUBLE FORMS OF VITAMIN A ON THE SERUM VITAMIN A, XANTHOPHYLL, AND CAROTENE CONCENTRATIONS IN CHILDREN WITH ALLERGIC STEATORRHEA

Patient	Age	I. U. Vitamin A per 100 ml. Serum*		Xanthophyll (gamma per 100 ml Serum)	Carotene (gamma per 100 ml Serum)
		Vitamin A Alcohol or Aldehyde	Vitamin A Ester		
K.K.	6 wks.	517	34	52**	47
	7 wks.		34		
	5½ mo.		587**	58**	238**
L.F.	3 mo.	445	245	45	32
	3 mo.		243		
D.W.	3 mo.	315	65	40	0
	7 mo.		191**	80**	27**
	7 mo.		215**		
F.J.	8 mo.	388	103	27	0
A.W.	2 mo.	646	342	55	21
	2 mo.	486			
P.M.	3 mo.		114	20	45
	2 yr.	771	338	70	120
D.B.	7 mo.	1391	144		
R.S.	2 yr.	570	152		
L.C.	6 yr.	920	49	152	18
M.L.	7 mo.	388	224	30	27
M.V.	10 yr.	1041	148	45	52
	10 yr.		1718**		
B.C.	9 mo.	365	205	20	147
L.S.	11 yr.	456	27		
D.C.	3 yr.	771	114	45	33
N.H.	3 mo.	414	163	17	103
D.P.	4 mo.	1748	144	10	28
D.M.	6 mo.	418	344	80	114
T.G.	5 yr.	813	243		
A.Me.	7 mo.	623	106	40	67
M.L.	3 mo.	399	346	100	186
J.M.	3 mo.	528	266		
Mean		655.1	182.7	49.9	61.2
Standard Error		76.2	26.1	12.5	12.5

* These values represent analyses of serum specimens obtained 4½ hours after the oral administration of a test dose of 7,000 I.U. of vitamin A per kilogram of body weight.

** These specimens were obtained after elimination of the offending food had resulted in clinical improvement.

1. Examination of feces for (a) eosinophilic leukocytes in strands of fecal mucus,^{16,17} (b) ova or parasites,¹⁸ (c) starch granules,¹⁹ and (d) qualitative and quantitative determinations for undigested fat.¹⁹

2. Examination of nasal secretions for eosinophilia.²⁰

3. Skin testing by the scratch method²¹ for presence of reagins to the common foods.

4. Vitamin A absorption tests, using both oily (ester) and the aqueous (alcohol or aldehyde) forms of Vitamin A.

Serum Vitamin A concentration determinations were made by a previously described method.²² Vitamin A absorption tests were performed as follows: After obtaining a fasting blood specimen for a baseline serum Vitamin A determination, the child was given an oral test dose of the ester form of Vitamin A (7,000 I.U. per kilogram of body weight). Four and a half hours later a second blood sample for Vitamin A concentration was withdrawn. In some instances, a third specimen was obtained seven and a half hours after the administration of Vitamin A. Several days later the test was repeated, substituting the alcohol or the aldehyde form of

ALLERGIC ENTERITIS—JOHNSTONE AND McCOORD

TABLE II. ABSORPTION OF THE ESTER AND ALCOHOL FORMS OF VITAMIN A BY NORMAL CHILDREN COMPARED WITH CHILDREN WITH VARIOUS FORMS OF THE CELIAC SYNDROME

	Number of Patients Studied	Vitamin A Ester		Vitamin A Alcohol	
		Mean I.U. Vit. A Concentration per 100 Serum	Standard Error of Means	Mean I.U. Vit. A Concentration per 100 Serum	Standard Error of Means
Newborns	35*	509.2	11.4	689.6	19.1
Older Children	13*	1569.7	72.4	819.2	41.9
Young Adults	12*	1303.0	57.2	1276.4	84.0
Idiopathic Celiac Disease	7*	142.5	55.2	256.8	114.3
Cystic Fibrosis of Pancreas	13*	126.5	27.8	1506.6	457.2
Allergic Steatorrhea	21	182.7	26.1	655.1	76.2

*McCoord²³

These values represent analyses of serum specimens obtained 4½ hours after the oral administration of a test dose of 7,000 I.U. of vitamin A per kilogram of body weight.

Vitamin A for the ester form. Using the criteria originally established by McCoord,²³ a minimum normal value for serum Vitamin A concentration four and a half hours after the oral test dose of either form of Vitamin A was arbitrarily set at 380 I.U. per 100 milliliters of serum. In each infant studied, efforts were made to rule out infectious diarrhea and cystic fibrosis of the pancreas by appropriate laboratory studies.

Barium swallow roentgen studies of the small intestines were performed in four children. Where feasible, the children in this study were followed after discharge in the general and in the pediatric allergy clinics of the Strong Memorial Hospital. Follow-up information was also obtained from those pediatricians whose private patients were included in the study.

RESULTS

During the three-year period, 1952-1955, there were 479 infants under two years of age admitted to the Strong Memorial Hospital. During this period sixteen of the infants admitted were found to have sufficient clinical and laboratory evidence to warrant a diagnosis of allergic enteritis. This was an incidence of 3.3 per cent of the total admissions to this ward. During this same period, 674 children between the ages of two and twelve years were admitted to the same hospital. In this age group there were five children with allergic enteritis, an incidence of 0.8 per cent.

Table I shows the effect of administration of the ester, alcohol and aldehyde forms of Vitamin A on the serum A, Xanthophyll, and carotene concentrations in subjects with allergic enteritis reported in this study. The significance of the Xanthophyll and carotene data are as yet unknown. Table II and Figure 1 compare Vitamin A absorption in members of this group with that of normals and of children with idiopathic celiac disease and cystic fibrosis of the pancreas.²³ From these data it may be seen

ALLERGIC ENTERITIS—JOHNSTONE AND McCOORD

that, whereas the mean serum Vitamin A concentration four and a half hours after oral administration of the ester form of Vitamin A is above the arbitrary normal value of 380 I.U./100 ml of serum in only normal infants and children, normal values are found after administration of the

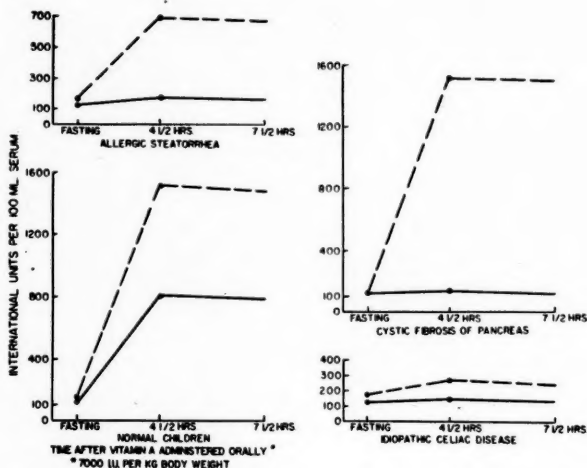


Fig. 1. Differential absorption of vitamin A ester and alcohol in children with celiac disease, cystic fibrosis of the pancreas, and allergic steatorrhea, compared to normal persons. The broken line represents serum vitamin A concentration values after oral administration of the alcohol form of vitamin A, and the solid line the values for the ester form of vitamin A.

alcohol or aldehyde form of vitamin A in only normal persons and those with cystic fibrosis of the pancreas and the children with allergic enteritis.

A positive family history of major respiratory allergy in either the siblings or parents of fourteen of the twenty-one children studied was found. Thirteen of the twenty-one have been found subsequently to have developed some signs of major allergy (atopic dermatitis, perennial allergic rhinitis, pollinosis or asthma). Five additional children have developed subsequent minor allergies (urticaria, drug sensitivities, other gastrointestinal allergic symptoms).

The foods, thought to be the causative agent by clinical history and observations, were milk in six infants, wheat in seven, vegetables in two, egg in two, and in four it was not determined. In one infant, both wheat and milk were thought responsible, and in another child milk and wheat were blamed initially. In the last child, a vegetable subsequently was also found to cause a flareup four months after the initial episode. Using routine scratch tests for the commonest foods, positive reactions were

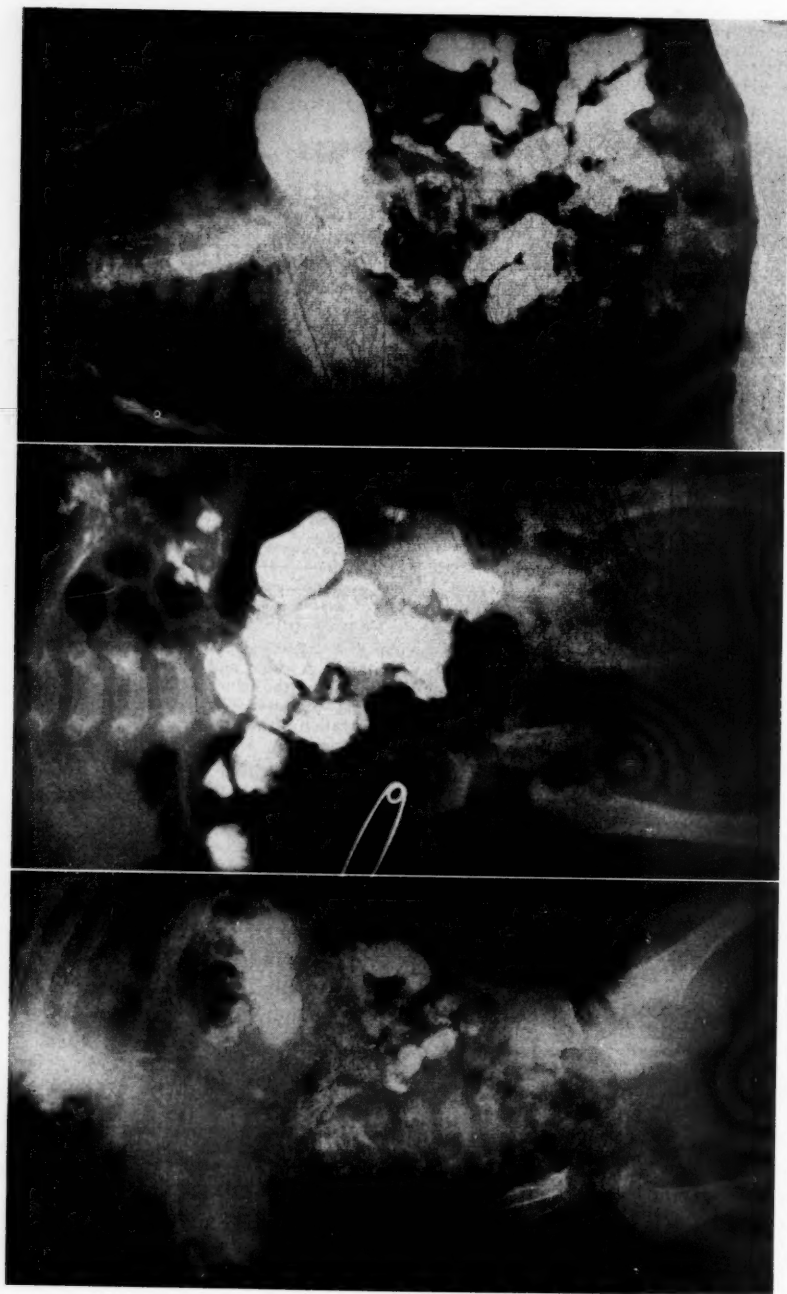


Fig. 2. (Left) Normal infant six months old. (Center) Three-month-old infant with allergic steatorrhea. (Right) Four-month-old girl with allergic steatorrhea.

found in only four infants. Three infants reacted to wheat, and one reacted to wheat and milk.

Figure 2 shows the characteristic pattern of the upper intestinal tract after barium swallow in two infants with allergic steatorrhea compared to that of a normal infant.

DISCUSSION

Whether prolonged diarrhea of allergic origin (with or without the other symptoms, which pediatric parlance usually lists as constituting the "celiac syndrome") should be labeled "the allergic celiac syndrome" is understandably an unsettled and debatable issue. All the children in this study at some time either had definite steatorrhea, as evidenced by clinical observation of the feces and increased fecal fat by chemical determination, or had evidence of interference with absorption of the ester form of Vitamin A. Abdominal distention occurred in the infants and children in this study who were under three years of age. Recurrent upper respiratory infections and apparent flareups of the diarrhea associated with respiratory infections were inconsistent findings in these children. The other symptoms commonly thought of as part of the "celiac syndrome," namely "failure to thrive and poor muscle tone," were present in those infants who presented the more acute and fulminating picture of allergic gastroenteritis,²⁴ especially those who had bloody mucoid diarrhea from milk intolerance in the first few weeks of life.

One possible advantage to use of the term "allergic celiac syndrome" would be to call attention to the fact that a certain percentage of children with "idiopathic celiac disease" may in fact be correctly diagnosed and might yield to specific therapy. This would reduce further the percentage of children with celiac symptoms, who before the writings of Anderson,²⁵ Gibbs²⁶ and Lowe and May²⁷ were all designated by the rather unsatisfactory term, "idiopathic celiac disease."

Similarity between not only the symptomatology but also the Vitamin A absorption curves of these children and those with cystic fibrosis of the pancreas has been previously described¹⁵ and should be kept in mind when either diagnosis is under consideration in infants under six months of age.

It should be pointed out that the failure to find fecal mucous eosinophilia does not rule out the possibility of this diagnosis. As in the examination of nasal secretions, a positive finding is significant. Failure to find eosinophils in fecal smears from these children usually means improper technique. One should make several smears, selecting only strands of mucus for staining. The mucus should be spread as thinly as possible on the slide, allowed to dry spontaneously and stained with either Wright's or Hansel's stain. The finding of more than three eosinophils per 100 leukocytes counted is indicative of gastrointestinal allergy. One must,

of course, bear in mind the remote possibility that malignant growths of the colon or parasitic infestations in the intestinal tract^{28,29} are also capable of producing eosinophilia in fecal mucus.

To diagnose the "allergic celiac syndrome" the following criteria should be met: (1) the child should have to some degree most of the characteristic symptoms of the celiac syndrome; (2) one should be able to associate at least indirectly, an allergic process with the given set of symptoms. To strengthen the basis for such a diagnosis, the following criteria should be met: (a) onset of diarrhea after the introduction of a new food, (b) improvement after its withdrawal, (c) family history of atopic disease, (d) history or occurrence of other atopic disorders in the patient, and, finally, (e) reproducibility of the syndrome by reintroduction of the offending food. The authors agree with Collins-Williams³⁰ that the occurrence of positive scratch or intradermal tests in these children is seldom found and is not a prerequisite for a diagnosis of allergic enteritis.

When the offending food is identified, it obviously should be removed from the diet. However, such identification may not be possible, even after it has been reasonably well established that the child's symptoms are on an allergic basis. If a carefully taken history does not suggest which food or foods are probably responsible for the symptoms, a safe procedure is to try an elimination diet, as recommended by Rowe.³¹ Rowe³² believes his elimination diets should be used not only as a therapeutic tool, but also as a diagnostic procedure when food allergy is suspected.

The role of wheat as an allergen suggests an interesting question. Is it possible that children whose "celiac disease" responds favorably to a "gluten-free diet" actually suffer from allergic steatorrhea? Recently, Dutch,³³ German,³⁴ Italian,³⁵ and English³⁶ writers have reported success by treating children with "celiac disease" with a "gluten-free diet." Our recent observation³⁷ of a young mother and her child, both of whom suffered from "celiac disease," suggested the possible parallelism of their condition with allergic steatorrhea. Both mother and son gave strong allergic histories and their Vitamin A absorption curves resembled those of the children in this study. The mother's symptoms subsided when she was placed on a gluten-free diet. Further support for this thesis is offered by Lips, one of the original promoters of the "gluten-free diet" therapy of celiac disease. In a recent paper³⁸ he noted that even better results were obtained when the "gluten-free diet" was combined with ACTH injections. This combination therapy would be likely to relieve sprue-like symptoms of allergic nature.

SUMMARY

During a three-year period, 3.3 per cent of infants and 0.8 per cent of children over two years of age admitted to the pediatric service of the Strong Memorial Hospital were found to suffer from allergic enteritis.

ALLERGIC ENTERITIS—JOHNSTONE AND McCOORD

The result of Vitamin A absorption tests on twenty-one infants and children with allergic enteritis, using the ester and alcohol or aldehyde forms of Vitamin A are described. Comparison of these data was made with similar data previously obtained from normal children as well as with those from idiopathic celiac disease and cystic fibrosis of the pancreas. A close similarity was found between the absorption of the two forms of Vitamin A in children with allergic steatorrhea and those with cystic fibrosis of the pancreas.

The criteria for making a diagnosis of allergic enteritis or "allergic celiac syndrome" are reviewed.

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MEDICAL JOURNALS AND THEIR MISSION

"Medical journals constitute the principal source of medical information today. Every year 3,000 medical books are published, 900 of them in the United States, and from 4,000 to 5,000 medical journals, nearly 1,500 of these in the United States. These journals are classified into three groups: monthly (33 per cent), bimonthly and quarterly (33 per cent), and the remainder annually, sporadically, or weekly. The volume of medical journals today is so great that there are special journals devoted to abstracts of abstracts appearing in other journals!"—F. MARTI-IBANEZ, *Books in the Physician's Life*, MD Publications, Inc., October, 1955.

DOES HONEY IN INFANT FEEDING CAUSE ALLERGY?

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THE USE of honey as a carbohydrate supplement in infant feeding has never enjoyed the popularity in this country that it has in other parts of the world. Since its source is natural and not synthetic, it contains a carbohydrate that is easily produced. Its cost has never been prohibitive; in fact, it is well within that of other carbohydrates used as milk modifiers.

There have been many studies conducted on its ease of digestion, influence on weight gain, control of gastrointestinal disturbances, and effect on hemopoiesis.¹⁻³ Vignec and Julio⁴ in 1954 conducted a most complete investigation. A total of 387 infants, divided into three groups, were fed honey, Karo syrup, and Dextri-Maltose No. 1 as a formula supplement. It was noted that honey-fed infants had a better average weekly weight gain, linear growth measures, and hemoglobin values, than those fed Karo syrup, but were no better in these respects than Dextri-Maltose-fed infants. Physiologic anemia requiring treatment occurred less in the honey-fed group. During a comparable period of time, Karo syrup-fed infants had more gastrointestinal problems than the honey and Dextri-Maltose-fed infants. It appears from this study and others that honey should be quite adequate as a carbohydrate supplement in infant feeding.

The medical literature reveals little as to allergic manifestations from the use of honey in infant feeding. Kuglelmass^{5,6} stated that honey could be used as a milk modifier in normal infants in moderate amounts, but could produce marked systemic reactions in allergic infants. Coca, Walzer, and Thommen⁷ quoted Mazai in their monograph. He had found that, if children (not infants) who had received horse serum over a period of four months were given honey, they developed severe respiratory and gastrointestinal symptoms. A comparable group of untreated children tolerated honey with no difficulty. Mazai could give no reason for his findings. A number of case reports of sensitivity to honey in adults have appeared in the literature as far back as 1884.^{8,9} The symptoms described are gastrointestinal, urticarial, asthmatic, and even anaphylactic. Sensitization was assumed to be due to the pollen of the flower from which the honey was obtained and to some type of protein from the bee itself that is secreted into the honey.

There are two important components in the chemical composition of

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HONEY IN INFANT FEEDING—STREM AND STOESSER

honey¹⁰ (Table I). They are protein 1.8 per cent and the undetermined portions 3.8 per cent (resins, gums, beeswax, coloring matter, volatile oils, vitamins, et cetera). These might account for sensitization to honey. Agranovsky¹¹ has indicated various sources of protein in honey that

TABLE I. THE CHEMICAL COMPOSITION OF HONEY*

Components	Percent
Levulose	39.10
Dextrose	34.00
Water	17.20
Proteins	1.80
Formic acid	1.10
Wax	.90
Mineral salts	.75
Dextrin	.45
Sucrose	.40
Malic acid	.30
Acetic acid	.20
Undetermined substances (Resins, gums, beeswax, coloring matter, volatile oils, vitamins, etc.)	3.80
	100.00

*From Luttinger, Paul: New York State M.J., 116:153 (Aug.) 1922.

might be of an antigenic nature. They are the nectar from plants which may be accompanied by a sensitization to a given plant protein, the presence of pollen in the honey, a protein of bee origin in the honey as a result of physiological change of the nectar into honey in the crop of the bee, a chemical introduced into the sealed cells for preserving the honey (similar to the sting poison of the bee), and propolis, which is a volatile product of protein nature and plant origin, present in the bee hive, giving the honey a definite odor.

Ingested protein can cause allergic symptoms in infants and adults alike. Undigested protein can be absorbed from the gastrointestinal tract of the infant as was shown by Schloss and Anderson¹² in 1923 and again by Lippard in 1939.¹³ This absorption provoked the formation of immune bodies that were demonstrated by precipitin, complement fixation and passive transfer tests. Permeability was greatest in marasmic infants and those suffering from diarrhea. They found that in infants with atopic eczema this was associated with a persistent state of tissue hypersensitivity. However, in a normal infant this absorption of protein is a physiologic and innocuous process. Therefore, it might be possible for an allergic infant to develop hypersensitivity to honey.

It is the purpose of this study to determine whether the use of a processed honey (strained or filtered) in infant feeding will cause untoward allergic manifestations. The honey used was taken from a common source in Minnesota and was harvested at various times and subsequently pooled. A qualitative analysis of the pollen particles revealed the unstrained honey to contain sweet clover (*Melilotus*), alfalfa (*Medicago sativa*), white clover (*Trifolium repens*) and many others in small amounts such as, *Artemisia* (sage) type, *Cichoriae* type, Sunflower (*Helianthus*), Violet (*Violaceae*)

HONEY IN INFANT FEEDING—STREM AND STOESSER

type, Catnip (*Nepeta cataria*), Buckwheat (*Fagopyrum esculentum*) and Iris (large monocot type). A quantitative analysis of the strained honey revealed a total of 18 grains of Melilotus in 15.4 sq mm, plus a few grains of alfalfa. The honey strainings contained a total of 381

TABLE II. ANALYSIS OF HONEY

1. Qualitative Analysis of Unstrained Honey	
A. Legumes:	B. Other Pollens (in small numbers)
1. Sweet Clover	1. Composites
2. Alfalfa	(a) Sage
3. White Clover	(b) Clethoriae
	(c) Sunflower
	2. Violet
	3. Catnip
	4. Buckwheat
	5. Iris
2. Quantitative Analysis of Strained Honey	
(Counted 10 sample fields on slide. Area of field 10 x 1.54 sq mm.)	
Total of 18 grains, all Sweet Clover in 15.4 sq mm.	
Sample also contained few grains of alfalfa.	
(Group B) didn't appear in sample fields.	
3. Quantitative Analysis of Honey Strainings	
(Same method as above)	
Total of 381 grains Sweet Clover in 15.4 sq mm.	
Total of 6 grains Alfalfa in 15.4 sq mm.	
Total of 1 grain White Clover in 15.4 sq mm.	
(Group B) didn't appear in sample fields.	
4. Protein Nitrogen Content	
A. Strained Honey	0.4461 mgm/N/gm.
B. Honey Strainings	0.5125 mgm/N/gm.

grains of Melilotus, 6 grains of Medicago, and 1 grain of Trifolium, in 15.4 sq mm. Ten sample fields were counted on a slide, and the area of the field was 10 x 1.54 sq mm. The protein nitrogen content of the strained honey and the honey strainings was 0.4461 mg nitrogen/gm and 0.5125 mg nitrogen/gm, respectively (Table II).

This honey was used as a 5 per cent carbohydrate supplement placed in the formula and fed to fifty-two infants. They represented well babies from the Community Health Clinics in Minneapolis, and were observed closely by the authors. The honey was given at the first clinic visit. The average starting age was five and one-half weeks and the study was continued for an average of twenty weeks. Of the fifty-two infants, twenty-four had a family history of allergy and twenty-eight had none. Four babies started the study with an existing allergic condition (eczema) and, of these, two had a family history of allergy.

RESULTS

The results are seen in Table III. In the group of infants with a family background of allergy, aside from the two that already had an existing allergic disease, nine developed an allergic manifestation (six had eczema and three had asthmatic wheezing for a short period of time). In the other group, aside from the two in whom allergic disease already was present, six developed an allergic manifestation (six instances of eczema, in one of which there was brief asthmatic wheezing). Seborrhic dermatitis occurred in six infants. There were no gastrointestinal problems of significance in the whole group. At the completion of the study, those infants who had shown allergic manifestations were skin-tested with unstrained honey, honey strainings and the pollens (sweet clover, alfalfa, white clover) shown to be present. This was done by the scratch method. None showed

HONEY IN INFANT FEEDING—STREM AND STOESSER

any positive reaction to the testing material which was employed. It is noted that fifteen (28 per cent) of fifty-two infants developed an allergic condition. There is no doubt that this figure is high, but only three out of fifteen could be shown to be clinically due to honey, as they improved

TABLE III. RESULTS OF FEEDING FIFTY-TWO INFANTS WITH HONEY AS A 5 PER CENT CARBOHYDRATE SUPPLEMENT IN THE FORMULA

	Positive—24	Negative—28
Family background of allergy	2 (eczema)	2 (eczema)
Pre-existing allergic disease	9 (6 eczema)	6 (5 eczema)
Developed allergic manifestations (28% of total infants)	(3 asthma)	(1 eczema and asthma)
Gastrointestinal disturbances	0	0
Allergic reactions to honey	1 (eczema)*	2 (eczema)*
Cutaneous tests on the infants with allergic manifestations		
1. Unstrained honey	Negative	Negative
2. Strainings	Negative	Negative
3. Pollens	Negative	Negative
(Sweet clover, alfalfa, and white clover)		

*Honey was discontinued and eczema improved.

when the honey was discontinued. They were three babies with eczema, of which one was in the group with a family history of allergy and two were in the other group. Honey was continued in the feeding of the four infants who had the existing allergic disease and in the twelve remaining infants throughout the study. During this period, other offending allergens were removed from the diet, and local therapy carried out, whereby the allergic manifestations subsided or disappeared.

DISCUSSION

Since honey comes from so many different plant sources, this study is by no means a complete answer as to whether honey can or cannot definitely cause allergy when used in infants' feeding. Yet, this type of honey is representative for Minnesota and the processing is the same as that for honey produced in other parts of the United States. It is even possible to process honey so that it is completely free of pollen. If it had been shown that the pollen in this honey was an allergenic factor, another study would have been carried out with a completely pollen-free honey. It was just by chance that this group of infants revealed such an exceedingly high incidence of allergy when only 10 per cent to 15 per cent of our total population is allergic. Close scrutiny of all the cases with allergic manifestations soon showed that the offending allergen was honey in only a few cases. The fact that the honey was continued in the allergic babies with appearance of no adverse symptoms may or may not substantiate the fact that the gastrointestinal tract of the hypersensitive infant is more permeable to unaltered protein. This would require more immunologic studies. Of some importance is the observation that there were substantially no gastrointestinal symptoms that could be related to the ingestion of the honey.

HONEY IN INFANT FEEDING—STREM AND STOESSER

SUMMARY

1. Allergic manifestations, resulting from the feeding of honey supplement to fifty-two infants, of whom twenty-four had a family background of allergy and twenty-eight had none, were determined.
2. Three infants developed an allergic condition which may have been due to the ingested honey. This observation could not be confirmed by cutaneous tests made with honey and pollens.
3. The honey produced no gastrointestinal disturbances in the infants of this study.
4. It can probably be assumed that the incidence of allergic manifestation due to the use of a processed honey in infant feeding is unusually small.

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The worst treatment for a patient with a functional disorder is to omit to listen to his story, to omit to examine him, to tell him there is nothing wrong with him, and to prescribe a sedative without a word of explanation. Patients with functional disorders who are treated in this way will fail to benefit just as any other patient will fail to benefit from such treatment. Many a "neurotic nuisance" is the product of his own doctor's attempts to save himself time and trouble.—Editorial: *The Medical Press*, 237:24 (January 9), 1957.

POTENTIATING THE EFFECT OF EPINEPHRINE WITH THE USE OF A GANGLIONIC BLOCKING AGENT

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IT IS well established that sympathomimetic drugs and parasympathetic blocking agents have some efficacy in preventing bronchial constriction. These pharmacologic actions have found application in the clinical management of bronchial asthma. The sympathomimetic drugs, such as epinephrine and ephedrine, undoubtedly present the best medical treatment we have to offer to the average bronchial asthmatic patient at the present time. Epinephrine causes bronchiolar dilatation and an increase in the rate and depth of respiration, permitting greater tissue oxygenation by augmenting oxygen intake. At the same time, the level of oxygen consumption of the tissue cells is raised.¹

Despite the efficacy of the drugs, there remains one drawback to their successful therapeutic application, i.e., the patient's increasing tolerance to the drugs after their use for variable periods of time. Thus, increasingly larger doses may be needed to give relief, and these may cause undesired side effects.²

The parasympathetic blocking agents have failed to fulfill clinically the promise provided by observation of their pharmacologic action;² e.g., the use of atropine for the allaying of asthmatic attacks has been disappointing. The recently reported efficacy of prantal methylsulfate and methantheline bromide^{1,3,4} raises the question whether these agents achieve a therapeutic response on the basis of their action on the parasympathetic nervous system or on the basis of some unrelated action or mechanism. We suggest that the results produced by methantheline bromide and prantal methylsulfate are due rather to their complete ganglionic blocking action. The rationale of this concept is to be found in Cannon's Law of denervation—"when in a series of efferent neurons a unit is destroyed, increased irritability to chemical agents develops in the isolated structure or structures, the effect of being maximal in the part directly denervated."¹ Denervation of effector organs receiving adrenergic nerves greatly enhances their sensitivity to epinephrine.²

It is suggested that these agents achieve their clinical effect in the asthmatic patient by sympathetic denervation—sensitizing the asthmatic

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EFFECT OF EPINEPHRINE—HIRSHLEIFER ET AL

patient to his own circulating epinephrine—rather than by a parasympathetic blocking action. With these observations and concepts in mind, we became interested in the possibility of alleviating epinephrine resistance and potentiating the effect of epinephrine and epinephrine-like compounds by utilizing a ganglionic blocking agent in conjunction with a sympathomimetic compound.

Part I

METHOD

Upon admission of a patient with acute bronchial asthma, the investigators were notified. A complete history was obtained and physical examination performed. Each patient admitted had previously been given epinephrine and intravenous aminophylline by the emergency room physician and had not responded. When seen by us, each patient was given epinephrine again and observed for twenty minutes. If no response occurred, the patient was then given tetraethyl ammonium chloride, either intramuscularly or intravenously, and observed for twenty to thirty minutes. Patients were observed for subjective and objective improvements. The latter was measured by diminution of rhonchi and wheezes and increased audibility of heart sounds. In addition, a careful check was made of the vital signs and side effects. Twenty minutes later, epinephrine 0.5 cc of 1:1000 aqueous solution was again administered subcutaneously. Patients were again followed for subjective and objective improvement.

CASE REPORTS

Case 1.—K. R., a forty-nine-year-old negro woman, was admitted to Kings County Hospital with a history of bronchial asthma of two days duration, rhinitis and cough, increasing dyspnea and wheezes in her chest. She had some asthmatic mixtures at home which did not afford her any relief. She had had similar attacks for the past three years, at least one of which she felt was brought on by exposure to dog dander. She since then had avoided exposure to dog hair. Her last severe attack was in January, 1955, and she was hospitalized for ten days. Since then, she had had a few mild attacks, relieved by pills given her at the clinic.

When seen in the emergency room she was given epinephrine subcutaneously and aminophylline intravenously without relief, and was therefore admitted.

Physical examination revealed a well-developed, well-nourished, forty-nine-year-old negro woman in rather severe respiratory distress.

Temperature was 100, pulse rate 124, respiration 46, blood pressure 120/84. The chest revealed high-pitched inspiratory wheeze and rhonchi throughout both lung fields; and sounded "tight" with prolonged-expiration heart tones that were distant. The remainder of the examination was unremarkable.

The patient was given 0.5 cc of 1:1000 epinephrine subcutaneously, and after twenty minutes there was no relief. She was then given 300 mg of tetraethylammonium chloride (TEAC) IV intravenously. Ten minutes after injection the patient stated that she was breathing easier and felt considerable improvement. The left lung field was considerably clearer than previously and heart tones were considerably more distinct. The respiratory rate dropped from 46/m to 36/m.

EFFECT OF EPINEPHRINE—HIRSHLEIFER ET AL

Fifteen minutes later (twenty-five minutes after TEAC) the lung fields on both sides were clearer than before and heart tones were good and well heard. Twenty minutes later the chest again began to tighten up with numerous wheezes and rhonchi. However, the patient stated she felt much better than before treatment. Within another thirty minutes, the chest again was "tight," similar to its condition prior to therapy, yet the patient stated she felt somewhat improved. Except for an initial drop in blood pressure to 90/68 after TEAC, there was no significant change in vital signs.

Summary.—Considerable subjective and objective improvement with use of 300 mg TEAC IV, preceded and followed by epinephrine. The effect, however, was of short duration. No side effects of significant degree were noted with use of IV TEAC.

Case 2.—L. E., a forty-eight-year-old white man, was admitted in status asthmaticus on December 28, 1955. He gave a history of bronchial asthma of eight years' duration. His attacks were infrequent initially but, since September, 1955, they had been more frequent. He was seen in the emergency room on several occasions. He was hospitalized at Kings County Hospital three times since September. He obtained slight relief with epinephrine plus aminophylline. He has never had an allergic or ear, nose and throat workup. His present admission was due to respiratory difficulty beginning on December 24, 1955, and which was only slightly responsive to epinephrine and aminophylline.

His medical history aside from asthma was normal. On admission his blood pressure was 120/80, pulse 100, respiration 20, and he was afebrile. Rhonchi were heard throughout the chest; heart sounds were barely audible. The remainder of the physical examination was within normal limits. Since he had received epinephrine 0.5 cc of 1:1000 subcutaneously in the emergency room prior to admission with slight transient effect, when seen at the ward he was given 300 mg TEAC intramuscularly. Within five minutes, there was definite subjective improvement; in twenty minutes the chest was quieter and the heart sounds could be more clearly heard. There were no other effects noted; his blood pressure and pulse rate remained stable.

Summary.—Definite improvement following TEAC, which lasted twenty minutes. No side effects were noted from the TEAC.

Case 3.—E. G., a thirty-five-year-old Negro woman was admitted with a history of known bronchial asthma since the age of thirteen. During adolescence she had two or three attacks per month, preceded usually by symptoms of an upper respiratory infection. She was treated by her physician with expectorants and bronchodilators, and responded well to treatment. At the age of twenty, her attacks began to become less frequent and recently has been getting one attack a year. She has no known allergies and her family history is negative for allergic manifestations.

The present illness began seven days prior to admission with symptoms of upper respiratory infection. Since then she had several asthmatic attacks, relieved by injections given her in the emergency room. About thirty hours prior to admission, however, her dyspnea became progressively intense. She did not respond to emergency room therapy, and was admitted.

Physical examination revealed a well-developed, well-nourished, thirty-five-year-old Negro woman in no acute distress at the time of this study. Her temperature was 98.6, pulse 86, respiration 24, and blood pressure 120/80. There was no cyanosis or clubbing. Pertinent findings were limited to the chest where there was

EFFECT OF EPINEPHRINE—HIRSHLEIFER ET AL

marked prolongation of expiration with generalized expiratory rhonchi and wheezes, most marked at the bases, and occasional fine expiratory rales in both mid-lung fields posteriorly. Heart sounds distant but not markedly so.

At 6:40, the patient was given 0.5 cc 1:500 epinephrine in oil. Following is her chart for the next two hours:

- 6:50—slight subjective, no objective, improvement.
- 7:00—slight subjective, slight objective, improvement.
- 7:10—fair subjective improvement, little to no objective improvement.
- 7:15—300 mg TEAC (IM). Blood pressure 120/80, pulse 86.
- 7:25—Blood pressure, pulse and respiration stable. No objective or subjective change.
- 7:35—Blood pressure 106/70, pulse 84, respiration 22. Slight subjective, no objective, improvement.
- 7:45—Blood pressure 112/74, pulse 84, respiration 22. Moderate subjective improvement, objective rhonchi and expiratory wheezes still exist, rales are no longer heard, expiration is definitely less prolonged.
- 8:00—Blood pressure 110/70, pulse 84, respiration 22. Moderate subjective improvement, no change in objective findings.
- 8:20—Blood pressure 110/70, pulse 84, respiration 22. As above.
- 8:40—Blood pressure 110/70, pulse 84, respiration 22. As above.
- 9:00—Blood pressure 110/70, pulse 84, respiration 22. As above.

Conclusion.—Slight subjective improvement with epinephrine in oil with no definite objective improvement. Definite subjective improvement after TEAC with only slight objective improvement.

SUMMARY AND CONCLUSIONS OF PART I

1. Eight of the ten patients studied showed moderate to marked subjective improvement following therapy.
2. Seven of the ten patients showed objective improvement which was of short duration.
3. It is our belief that chemical blocking of autonomic ganglia may indeed play a role in returning responsiveness to epinephrine-fast asthmatic patients. We do not feel that this work provides the answer to the problem, but we were encouraged by the transient relief obtained in most of our patients and feel that more investigation along these lines is warranted.

Part II

A CLINICAL COMPARISON OF THE EFFECTIVENESS OF A GANGLIONIC BLOCKING AGENT WITH AND WITHOUT EPHEDRINE COMPOUND IN BRONCHIAL ASTHMA

With these observations in mind, an investigation was undertaken to determine the possibility of: (a) Potentiating the effect of epinephrine and similar compounds, and (b) preventing the development of tolerance by utilization of epinephrine-like compounds in combination with a ganglionic blocking agent.

It is the intent of this communication to report upon the comparable

efficacy of a ganglionic blocking agent, (Methium*) and a widely utilized ephedrine compound (Tedral*) when given singly and in conjunction with each other in the treatment of bronchial asthma.

The medications utilized in this investigation were contained in capsules identical in appearance. The size was number "O" and the color pink. Each type of capsule was identically packaged in amber colored bottles. The only identification or code used appeared on the outside label of each bottle and this code was "A," "B," or "C."

Capsule A contained Hexamethonium Chloride 125 mg (Methium); Capsule B contained Theophylline 2 gr (130 mg), Ephedrine $\frac{3}{8}$ gr (25 mg) (Tedral), Phenobarbital $\frac{1}{8}$ gr (8 mg); Capsule C contained Theophylline 2 gr (130 mg), Ephedrine $\frac{3}{8}$ gr (25 mg) (Tedral with Methium), Phenobarbital $\frac{1}{8}$ gr (8 mg), Hexamethonium Chloride 125 mg.

The investigation was performed in the Allergy Clinic of Kings County Hospital. The patients were mainly of long-standing attendance at this clinic. They were rotated consecutively on capsule "A," "B," and "C," taking each type of medication for approximately four weeks. We attempted to have one-third of the patients on each drug combination at the same time to overcome seasonal influences. The patients were examined for both subjective and objective changes in their asthmatic status and interrogated to determine if any side effects resulted from the medications.

In addition, pulmonary function tests were performed upon them at various intervals to determine the degree of disability of the patient, to follow the progress of the disease in individual cases, and to assay the effectiveness of the various drugs.⁵⁻¹⁰ The values in normal subjects derived by Baldwin, Cournand and Richards were taken as our standard normal values.¹¹

In the present study, serial determinations of the one-second timed vital capacity were performed weekly on each patient. Recently, Gaensler¹⁴ has found that timed vital capacity measurements provide a method for indicating the very appreciable slowing of the expiratory phase commonly found in bronchial asthma and emphysema. This method of testing was selected because of its simplicity and low cost.

The vital capacity is the maximal volume of gas that can be expired from the lungs by forceful effort after a maximal inspiration.¹² It may be normal or decreased in patients with bronchial asthma, as compared with the predicted normal.^{5,7,8} Cournand¹³ described a method of graphic registration of breathing by means of a modified basal metabolism

*Acknowledgment is made to Warner-Chilcott Laboratories for supplying the Tedral and Methium for this study.

EFFECT OF EPINEPHRINE—HIRSHLEIFER ET AL

apparatus and noted that a change in the form of deep breathing, particularly retarded expiration, revealed early stages of pulmonary emphysema in bronchial asthma.

METHOD

A simple attachment to the ordinary dial-type vital capacity machine^{14,15} records automatically the total vital capacity and the fraction of the total volume exhaled during the first second, first two seconds, or first three seconds of the maximal expiratory effort. The onset of expiration automatically initiates the timing cycle. Normal persons are capable of exhaling 83, 94, and 97 per cent of the total vital capacity during one, two and three seconds. With restrictive defects, the total vital capacity is reduced, but the timed percentages remain normal. In the presence of airway obstruction or impaired elastic recoil, small reductions of total vital capacity are accompanied by marked decreases in timed capacities. Unlike the vital capacity, the timed capacities correlate well with maximal breathing capacity, air velocity index, and the ratio of the residual volume to the total lung capacity.^{15,16}

RESULTS

Twenty patients were tested by the preceding methods. A double evaluation was made of each patient. The first was a clinical determination of how the patient felt, and included a physical examination. The second was on the basis of one second timed vital capacities. Each method of response was graded as follows: No improvement=0, slight improvement=1, moderate improvement=2, and excellent improvement=3.

Our conclusions were reached by adding the above numeric response of each drug. For example:

ILLUSTRATIVE CASES

Case 1.—E. A. is a forty-three-year-old white woman who has had bronchial asthma since 1952. In 1946 she underwent a thyroidectomy for hyperthyroidism, and in 1953 was told that she was euthyroid. She has been unable to work for

TABLE I. EXAMPLE OF NUMERICAL RESPONSE TO EACH DRUG. PATIENT E. A.

Capsule	Clinical Assessment	Timed Vital Capacity	Total
A	2	1	3
B	2	2	4
C	3	3	6

the past five years because of exertional dyspnea. She is separated from her alcoholic husband and takes care of a daughter, aged fifteen. The daughter has periodic episodes of chest pain, judged after careful study to be psychosomatic. The patient was often upset because of the family situation as well as her own illness and relative incapacity. Her medications included ACTH, cortisone and

EFFECT OF EPINEPHRINE—HIRSHLEIFER ET AL

prednisone, as well as Quadralin and other bronchodilators at one time or another. Asthmatic attacks were usually more severe during menstruation, and were often precipitated by upper respiratory infections. At the start of the study she was taking 30 mg prednisone daily. This dose was gradually reduced to 15 mg and she was given meprobamate 1600 mg daily which allayed her anxiety.

On the basis of an average of individual performances, this patient experienced some improvement on A and B, but preferred C.

TABLE II. RESULTS WITH PATIENT E. A.

Capsule	Vital Capacity	First Second
A	2063	900
B	2700	1275
C	3000	1700

Case 2.—E. O'D is a fifty-one-year-old white man who has had bronchial asthma since 1954, and at the present time has a continuous wheeze. In the past he has been treated with desensitization injections, Quadralin, and a cough medicine. A trial of cortisone gave some relief one year prior to this study. At the start, he was placed on 10 mg prednisone for two weeks with some improvement, but this was discontinued in order to evaluate A, B, and C. He felt some improvement on B and C, but preferred B.

TABLE III.
RESULTS WITH PATIENT E. O'D.

Capsule	Vital Capacity	First Second
A	2775	1300
B	2450	1000
C	3216	1683

RESULTS OF TWENTY CASES

The results in the twenty patients with bronchial asthma (Table IV) treated with the ganglionic blocking agent and the ephedrine-like compound (Methium and Tedral) showed that the action of the ephedrine compound was reinforced by the ganglionic blocking agent. This result

TABLE IV.
RESULTS WITH TWENTY PATIENTS

Medication	Clinical Response	One Second Timed Vital Capacity	Totals
A	12	18	30
B	33	26	59
C	40	29	69

substantiates Cannon's conclusion that denervation of a sympathetically innervated structure sensitizes this structure to epinephrine or epinephrine-like compounds. It is hoped that in the future this same principle can be

EFFECT OF EPINEPHRINE—HIRSHLEIFER ET AL

utilized to prevent or at least retard, the development of progressive resistance in the bronchial asthmatic patient to epinephrine or related drugs.

The side effects in those cases in which the ganglionic blocking agent was used were the same as those reported in the past.¹⁷ They included constipation, blurred vision, slight vertigo, and difficulty in urination. However, because of the small dosage of the blocking agent used, the side effects were correspondingly mild, and in only one patient was it necessary to discontinue the drug because of side effects.

SUMMARY AND CONCLUSIONS

Twenty cases of bronchial asthma were tested for their therapeutic response to a ganglionic blocking agent (Methium), an ephedrine compound (Tedral) and a combination of both. Scoring of improvement both by clinical assessment and by timed vital capacities shows a distinct advantage for the combination of these drugs, rather than either drug alone. When the drugs were used singly, the ephedrine compound (Tedral) was very much superior to hexamethonium chloride (Methium).

ACKNOWLEDGMENT

Grateful acknowledgment and indebtedness to Solomon Slepian, M.D., for his co-operation and helpfulness in making this investigation in the Allergy Clinic of Kings County Hospital possible.

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"WHEN THE STUDENT HAS MASTERED A DEFINITE TECHNIQUE, WHAT THEN?"

"The danger (say Davis and Nelson) is that he will over-estimate rather than under-estimate the value of this equipment. Statistical methodology is no magical, or even mechanical, instrument that automatically grinds out valid conclusions and allows the suspension or avoidance of personal judgment. Indeed, it may be said flatly that a statistical conclusion is no better than the judgment of the statistician who produced it. Knowing what tool to employ is just as important as knowing how to employ it. The second can be taught, but the first must be learned. The novice will tend to think that the more high-powered his methods, the more cogent his analysis. This is not at all necessarily true. A scatter diagram may well yield more information than a correlation coefficient. The fact that the latter may be carried to several decimal places gives a spurious appearance of accuracy, while it may really be concealing such facts as that the relationship is curvilinear or that some of the observations are evidently grossly distorted. In such a case, the apparently crude method is really enlightening, the apparently precise method is really deceptive. Very often a free hand curve drawn through a graph will tell as much about the trend as will ever be revealed by logistics or quintics. Again, the methods may be too refined for the data."—HAROLD T. DAVIS and W. F. C. NELSON, *Elements of Statistics*. Bloomington, Indiana, 1935, p. 334.

ANAPHYLAXIS AND THE NERVOUS SYSTEM. PART IV.

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IN PREVIOUS communications,¹⁻³ we reported on the inhibition of anaphylactic shock through bilateral focal lesion of the tuberal region of the hypothalamus produced by the Horsley-Clarke stereotaxic apparatus modified by Szentagotai. These lesions also produce inhibition of antibody production. This, however, does not explain completely the anti-anaphylactic effect. The lesions also modify the second (nonspecific) phase of anaphylactic shock. We showed that the surgical intervention influenced neither antigen-antibody union nor the liberation of tissue material during shock. (Our investigations concerning the liberation of tissue material will be published at a later opportunity.) We had, then, to consider the possibility of an increased resistance of the tuberal-injured organism to the tissue material liberated through the shock.

A dominant role among the tissue materials liberated during anaphylactic shock is played by histamine and, therefore, the histamine resistance of the tuberal-injured organism was examined in the experiments here presented.

I. Effect of Histamine on the Rectal Temperature of the Tuberal-injured Guinea Pig.

We tuberally injured¹ guinea pigs weighing 300 to 400 g. On the seventh day following tuberal lesion, we injected subcutaneously 0.5 mg/kg of body weight of histamine dihydrochloride into the fifteen tuberal-injured and the seven normal animals retained as controls.

At the moment of the histamine injection, and twenty, forty and sixty minutes later, we measured the rectal temperatures of the animals. The results are shown in Figure 1. It will be seen that the fall in temperature in the tuberal-injured guinea pigs was less and occurred much later than in normal animals.

II. Effect of Tuberal Lesion of the Hypothalamus on Histamine Shock in the Guinea Pig

In preliminary experiments, we determined the 100 per cent lethal dose of histamine for guinea pigs. It was found to be approximately 5 mg/kg of body weight. In the experiments described here, we injected 7 mg/kg of body weight of histamine base, that is, approximately one and one-half times the 100 per cent lethal dose.

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ANAPHYLAXIS—SZENTIVANYI AND SZEKELY

Two groups of guinea pigs were used. The first contained eighty-four tuberal-injured and thirty-five control guinea pigs. Distribution of sex and weight in the injured and the control groups was the same. Injection was given seven days after the tuberal injury.

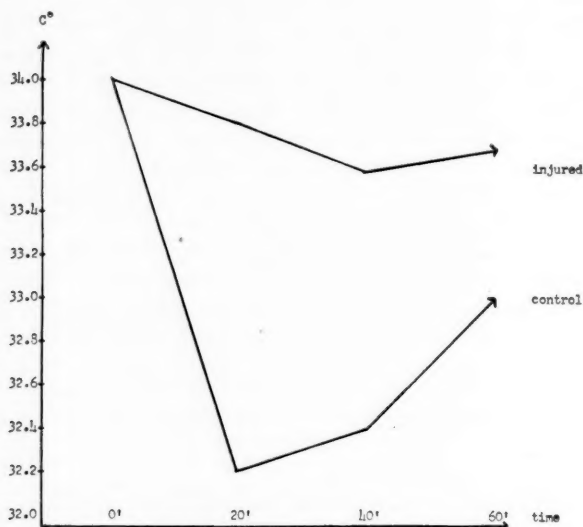


Fig. 1. Mean temperature after injection of 0.5 mg histamine dihydrochloride in fifteen tuberal-injured and seven normal guinea pigs.

RESULTS

The characteristic symptoms of histamine shock developed equally in tuberal-injured or control animals. The control animals, however, died after the histamine injection within an average of ten to fifteen minutes. By contrast, 34 per cent of the tuberal-injured animals survived the poisoning after severe shock symptoms lasting many hours. Six weeks after the first shock provocation, we gave the surviving animals the same dose of histamine. They all died with the exception of one animal, which later died during a third histamine shock produced three weeks later. The anatomic (postmortem) observation showed that tuberal lesion had been obtained in seventy-seven and extrahypothalamic lesion in seven cases (Table I).

When comparing the period of survival of the tuberal-injured and the control animals, it appeared that even when the tuberal-injured animals died, they often survived considerably longer than the control animals (Table II).

From the result of repeat injections, it appeared that the greater

ANAPHYLAXIS—SZENTIVANYI AND SZEKELY

resistance of the tuberal-injured animals was transitory. In order to obtain further evidence on this point, a second experiment was made.

The second group contained forty-three tuberal-injured and twenty-seven control guinea pigs. The experimental procedure was the same as

TABLE I. SHOCK PROVOCATION SEVEN DAYS AFTER TUBERAL LESION

Localization of Lesion	Number	Died	Survived	Per Cent of Survival
Tuberal region	77	51	26	34%
Extrahypothalamic region	7	7	0	0%
Control group	35	35	0	0%

TABLE II. SHOCK PROVOCATION SEVEN DAYS AFTER TUBERAL LESION DISTRIBUTION OF SURVIVAL TIME IN PER CENT

Time	5'	10'	15'	20'	30'	60'	2 h	5 h	10 h	More than 10 h
Tuberal region	17	34	4	3	1	4	1	1	1	34
Extrahypothalamic region	43	29	14	14	—	—	—	—	—	—
Control group	55	20	10	6	3	6	—	—	—	—

TABLE III. SHOCK PROVOCATION SEVEN WEEKS AFTER TUBERAL LESION

Localization of Lesion	Number	Died	Survived	Per Cent of Survival
Tuberal region	31	31	0	0%
Extrahypothalamic region	12	12	0	0%
Control group	27	27	0	0%

before, except that the shock was produced seven weeks after the operation. Both operated and control animals died within about the same period of time. Postmortem observation established tuberal lesion in thirty-one, extrahypothalamic lesion in twelve of the animals operated on (Table III).

CONCLUSIONS

1. Histamine resistance in the tuberal-injured guinea pig is increased, judging both from the rectal temperature test and the survival rate and time.

2. The protection, however, is only transitory and disappears seven weeks after tuberal lesion.

3. Increased histamine resistance appears to be a factor in the anti-anaphylactic effect of tuberal lesion.

ANAPHYLAXIS—SZENTIVANYI AND SZEKELY

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THE ARTIST AND THE SCIENTIST

"The artist cannot reproduce every aspect of nature or realize every dream of his mind; he must choose, choose, choose. Even so the scientist cannot study every fact and attack every problem; he must choose and choose and choose again. His activities are continually dominated by the need of selection; they may be suddenly exalted by a wise choice, or jeopardized, even nullified, by a wrong one. Genius in science as well as in art includes, as one of its essential elements, that uncanny quality, the ability to select the most characteristic lines or colors, melodies, or harmonies, or the salient fact, the fertile problem, the 'crucial' or enlightening experiment. Granted that selection is even more fundamentally and continually important for the artist than for the scientist, that is, that artistic creation is far more arbitrary than scientific creation, the difference between them is quantitative rather than, as is generally believed, qualitative.—GEORGE SARTON, *The Study of the History of Science*. New York, Dover Publications, Inc., copyrighted, 1936.

INFLUENCE OF pH OF EXTRACTANT ON THE ELECTROPHORETIC AND ANTIGENIC COMPOSITION OF LOW RAGWEED EXTRACT

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ALTHOUGH it might be anticipated that the nature of the extractant would determine the quality and quantity of materials withdrawn from pollen granules, little if any attention has been given this matter. Nor do allergists employ a uniform extracting fluid in preparing their therapeutic solutions. The purpose of the present investigation on ragweed pollen was to study the effect of pH on extraction with solvents that varied in pH from 3 to 8.6. The extracts were examined by electrophoretic analysis (Tiselius, free electrophoresis^{1,2}) at pH 8.6 and 5.5. They were also examined for specificity differences by the cross-test technique of passive sensitization in the skin of normal human subjects. Although such comparisons of electrophoretic composition and allergic specificity (for two crops of pollen) revealed that the character of the extract does change in certain particulars with the pH of the extractant, there was essentially no correlation between the two sets of analytical data.

PRINCIPAL UNDERLYING THE ELECTROPHORETIC METHOD

Moving boundary electrophoresis, an analytic procedure that has been applied to ragweed pollen by a number of investigators,²⁻⁷ is based on the migration of charged components in an electric field. Under the action of an external electric field, an initial boundary between the solution under investigation and a buffer solution of the same pH and conductivity separates into a series of boundaries. Each of the latter moves at a rate that is proportional to the mobility (velocity per unit field strength) of the related component. The gradient that develops as the concentration of the component falls to zero during electrophoresis produces a refractive index gradient that may be observed by appropriate optical techniques, utilizing the schlieren diaphragm or a cylindrical lens. The boundaries are thus displayed and photographed as a series of peaks, the heights of which measure the refractive index gradients and the areas under which are proportional to the concentrations of the several components. It must be noted, however, that in many instances these peaks are not particularly sharp and that overlapping may also occur, the latter sometimes being observed as a shoulder on an adjoining peak. To determine the characteristic mobilities of the several constituents of a mixture, photographs are

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LOW RAGWEED EXTRACT—LOVELESS AND WRIGHT

taken periodically during the analysis so that the distances they move in a given time (cm./sec.) can be calculated for the constant field strength of one volt/cm.

Shortly after electrophoresis was developed, it was applied to the study of such mixtures as blood serum. However, the patterns associated with the two limbs of the cell were often not symmetrical. For theoretical reasons which will not be discussed here, it soon became conventional to derive the analytical mobility data from the descending patterns. Thus, in the case of serum, mobilities and area measurements were based on resolution occurring in the cathodal limb of the cell where the negatively-charged proteins, or anions, were moving down into the original sample in the lower portion of the limb. In other words, migration was toward the anode, or positive pole, that was connected to the upper part of the opposite limb.

For a more complete discussion of the theory and application of electrophoresis, the reader is referred to Alberty¹ and Becker.²

The first studies of pollen extract revealed the existence of a major, essentially stationary peak and as many as six minor, pigmented components bearing negative charge at pH 4.5 in .02 molar sodium acetate buffer.³ Newell⁵ soon discovered two additional components of positive charge in water extracts of ragweed pollen that were analyzed at pH 4, ionic strength .05. Becker² and Loveless and Timasheff,⁷ later undertook to analyze low ragweed extract over a wide range of pH varying from 3 to 8.6, and encountered a mixture of components carrying charges of opposite sign. Indeed, the pH 5 acetate buffer extracts studied by the latter workers regularly exhibited three components of positive charge when examined electrophoretically at pH 7.5 or less, ionic strength 0.1; and a fourth component of low positive charge could be resolved from the major, stationary peak if analysis were extended to 11 hours. There were also the several pigments of opposite charge that had been described by others.²⁻⁶

The effect of pH on the removal of cationic and of anionic materials from low ragweed pollen will now be analyzed from the electrophoretic as well as the immunologic viewpoints.

MATERIALS AND METHODS

Antigen.—Two crops of low ragweed pollen (*ambrosio artemisiifolia* or *a. elatior*) were examined, both supplies being harvested and promptly sun-dried by F. Hodgson of Verona, New Jersey, one in 1952 and the other in 1954. To provide adequate concentrations of minor constituents, it was necessary to extract as many as 30 gms of ether-defatted pollen per 100 ml of extractant. With the exception of a ten-minute preparation made with distilled water at 40° C, all extractions were carried out at about 4° C and were facilitated by automatic stirring for eighteen hours. Pertinent information concerning the composition of the various extractants and other preparatory conditions is presented in Table I. After the supernate

LOW RAGWEED EXTRACT—LOVELESS AND WRIGHT

TABLE 1. POLLEN EXTRACTION

Pollen Crop	Extractant				Conditions of Extraction		pH of Final Extract
	Type	pH	Ionic Strength	Composition	Temperature	Duration	
1952	alkaline extracting fluid	8.4	0.12	.09M NaCl	4° C.	18 hrs.	6.2
1954				.03M NaHCO ₃			6.6
1952				.04M phenol			6.0
1952	phosphate buffer	7.5	0.07	.005M NaH ₂ PO ₄	4° C.	18 hrs.	5.8
1954				.021M Na ₂ HPO ₄			5.9
1952							5.8
1954	distilled water	ca. 6 to 7			40° C.	10 mins.	5.8
1952							5.4
1954							5.4
1952	acetate buffer	5.0	0.10	.010M NaAc	4° C.	18 hrs.	5.4
1954				ca. .05M HOAc			5.4
1952							4.3
1952	glycine HCl buffer	3.0	0.10	.50M glycine .10M HCl	4° C	18 hrs.	4.3

had been passed through a bacteria-retaining, fritted glass filter, one aliquot was tested at once in a pH-meter while another was analyzed by electrophoresis within two to seven days. Immunologic examination was completed within twenty-four days, specimens being stored meanwhile in the cold.

Each extract was labeled according to its content of phosphotungstic-acid-precipitable nitrogen, 0.1 mg PtaN being called 10,000 "protein" N units. (For those who employ the weight-by-volume designation, this is equal to 1-85 extract, while for the total N standard the corresponding figure is about 0.126 mg). Our 25 to 30 gms per cent extracts ranged from 235,000 to 294,000 protein N units in strength.

Electrophoresis.—To insure adequate concentration of minor components, a portion of each preparation was reduced in volume by exposure to prolonged fanning in a cellophane sack. The concentrate was then dialyzed for twenty hours against 124 volumes of the buffer selected for analysis, to equilibrate the pH and conductivity of the two solutions. There was always some loss of dialyzable pigment into this buffer. The final protein concentration of the residual sample in the sack was about 0.9 gm per cent.

Free electrophoresis was employed for analysis at pH 8.6 in barbital buffer, ionic strength 0.1, and again at pH 5.5 in acetate buffer of the same ionic strength. A Perkin-Elmer apparatus served for all the studies, voltage being measured with a potentiometer. In the case of the 1952 pollen extracts, 4.5 v./cm were applied, whereas a slightly greater field strength of 5.8 v./cm was chosen for the 1954 preparations in an effort to facilitate resolution. The areas beneath the various peaks in the photographs were measured with a planimeter, the contribution of each to the overall area

of the pattern being expressed in per cent, according to the practice of Tiselius and Kabat.⁸

In the present study, each extract was examined in both the cathodal and the anodal arms of the cell, sometimes in separate analyses and sometimes in a single electrophoretic experiment. In most instances, we employed what might be called half-way compensation. In this modification of the standard procedure, the original boundary between the sample and the buffer is artificially lowered in the cell to facilitate the simultaneous observation of the moving boundaries provided by substances of either charge. Examination of both limbs was instructive not only because constituents of unlike sign exist in pollen extracts, but also because they form patterns that are more complex when the materials are ascending into the buffer than when they are descending into the original sample in the lower portion of the analytical cell.

Interpretation of Electrophoretic Findings.—Arbitrary symbols have been assigned the various peaks encountered during analysis, the most complex configurations being chosen for the purpose. These were associated with the ascending patterns formed at pH 8.6 by the 1952 extracts. Whereas attention was focused on the anodal limb when substances of negative charge were under consideration, the opposite limb served when components of positive charge were being analyzed. In addition to these 180-minute analyses that were done with half-way compensation, a second examination at the same pH but with conventional starting boundaries was carried out for 360 minutes on the 1952 preparations to separate the components of positive charge. Meantime, the major peak which was noted in all patterns and which exhibited essentially no charge was arbitrarily selected from the cathodal patterns when symbols were being assigned. The most mobile of the positively-charged substances was given the symbol R-1 (ragweed component No. 1), while a slower peak adjacent to it was labeled R-2. No allowance was made for an undetected peak of even lower mobility and positive charge which was encountered by Loveless and Timasheff⁷ during their analyses of pH 5 extracts. Inasmuch as the major, "stationary" component fell into the next position, it was designated R-3. (Included in this large peak is a contribution from the usually small, so-called epsilon boundary in the cathodal pattern and a corresponding, usually larger delta boundary in the anodal pattern. These "false" boundaries are not due to real components but reflect density differences, above and below the positions of the starting boundaries, which develop during electrophoresis.) Five components of negative charge brought the total number of apparent components to nine. A tenth could possibly have been resolved from the major peak by extending analysis to eleven hours.⁷

When electrophoresis was undertaken at pH 5.5, movement of the negatively-charged materials was, as anticipated, slower, owing to the

reduction of charge and of consequent mobility at the lower pH. In fact, fewer anionic peaks were resolved from the extracts. One component that had been detected at pH 8.6 now appeared to have been brought to its isoelectric point so that it was obscured by the major stationary peak, R-3. Certain others appeared to have remained with components that were adjacent to them during the analyses at pH 8.6. Under the circumstances, it was at times difficult to allot the symbols to the pH 5.5 components. However, the designations given the peaks in the pH 8.6 patterns were arbitrary and provisional, and were introduced only to simplify discussion of the electrophoretic findings. At any rate, errors in transposition of symbols to the pH 5.5 analyses would have had no influence on our conclusions concerning the effect of extractant pH on the electrophoretic constitution of ragweed extract.

Immunologic Comparisons.—Preliminary trials in normal skin revealed that 2,500, and in some instances 1,000 units of extract would exhaust all the skin-sensitizing activity possessed by 1 ml of VON standard reaginic serum, the twenty-four-hour challenges being made with 1,000 unit homologous solution. It was further established that .02 ml of a 160-unit sample of any of the preparations was about the least that would evoke our three-plus wheal and flare response in control areas that had been prepared with 0.1 ml of 1:2 VON serum. With this information, it was possible to plan reliable cross-tests among the various pollen extracts.

The alkaline-extracting fluid preparation of the 1952 pollen, for example, was mixed with an equal volume of VON serum. The mixture was then injected endermally in a volume of 0.1 ml into six sites along the dorsal aspect of the thorax of a normergic individual. An adjacent column received a corresponding mixture of VON serum and phosphate buffer extract, the latter being required in only 1,000-unit rather than the customary 2,500-unit strength, according to the preliminary neutralization trials. A third column was set up with a 2,500-unit sample of the eighteen-hour, water extract and the standard reaginic serum. When the rest of the neutralizing mixtures had been injected, a final site in each column was prepared with a mixture containing VON serum and isotonic saline solution. All areas, including these control sites, exhibited prompt whealing that was recorded as three plus (central blanching that measured about 1 cm in diameter, surrounded by a bright red flare about 2 cm in width). Although such reactions as those encountered in the control sites are little understood, in the present instance they increased the value of the control tests carried out on the following day. The basis of this remark is that whealing tends to render the area temporarily hyporesponsive^{9,10} to later stimulation with a reagin-antigen system. Consequently, any such refractoriness in the skin prepared with our active mixtures would theoretically have been balanced by the nonspecific irritative responses elicited by the serum-diluent mixtures. Each location was dotted with an indelible pencil

TABLE II. ELECTROPHORETIC ANALYSES IN BARBITAL BUFFER AT pH 8.6, IONIC STRENGTH 0.1

LOW RAGWEED EXTRACTS PREPARED AT GRADUATED pH LEVELS

Composite of Data Provided by Separate Analysis of Negatively and of Positively Charged Components in Ascending Limbs

Extractant	Final pH of Extract	Component R-1		Component R-2		"Immobile" Component R-3	Component R-4		Component R-5		Component R-6		Component R-7		Component R-8		Component R-9	
		Area in %	Mobility (U)	Area in %	Mobility (U)		Area in %	Mobility (U)	Area in %	Mobility (U)	Area in %	Mobility (U)	Area in %	Mobility (U)	Area in %	Mobility (U)	Area in %	Mobility (U)
Alkaline extracting fluid at pH 8.4 Phosphate buffer at pH 7.5 Water for 18 hours at pH 6.7 Water for 10 mins. at pH 6.7 Acetate buffer at pH 5 Glycine buffer at pH 3	6.2 6.0 5.8 5.8 5.1 4.3	Resolution in cathodal limb during 360 mins.†																
		1952 pollen																
		Resolution in cathodal limb during 180 mins.																
		1952 pollen																
		Resolution in anodal limb of cell during 180 minutes																
		1952 pollen																
		Resolution in anodal limb of cell during 180 minutes																
		1954 pollen																
		Resolution in cathodal limb of cell during 120 minutes																
		1954 pollen																
		Resolution in anodal limb of cell during 150 minutes																
		1954 pollen																
Alkaline extracting fluid Water for 18 hours pH 6.7 Water for 10 mins. at pH 6.7 Acetate buffer at pH 5	6.6 5.8 5.8 5.4	Resolution in cathodal limb of cell during 120 minutes																
		1954 pollen																
		Resolution in anodal limb of cell during 150 minutes																
		1954 pollen																
		Resolution in anodal limb of cell during 150 minutes																

* x 10⁻⁴ cm./sec./v./cm.

†This supplementary analysis to resolve the positively charged components was made under conditions of conventional compensation of the starting boundaries; all others at half-way compensation.

**Inasmuch as R-4 had not as yet been resolved, the area measurement is somewhat excessive.

so that the challenge injection to be given in twenty-four hours could be accurately directed along the original needle track.

It was a necessary prerequisite that the challenge response to the homologous extract at twenty-four hours be negative, indicating that the corresponding reagins had been neutralized by the *in vitro* allergens. A negative challenge reaction to the 160-unit preparation of any other extract revealed that the latter possessed no significant amount of any antigens not also present in the desensitizing extract. A partial challenge response, on the other hand, betokened the existence in the testing solution of certain activities which were present in the neutralizing extract and of others which were absent from this extract. The degree of curtailment was judged by the response of a control site to concurrent test with the standard volume of .02 ml of the same testing material. When a challenge evoked a full reaction, it could be concluded that its activity rested chiefly or completely on allergens which were lacking in the neutralizing extract. After all the data were recorded, it was easy to discern the relative complexity of any two preparations by noting the outcome of mutual crosstests. No corrections had to be made for irritating qualities in the challenging solutions since none were encountered during concurrent tests in unprepared skin.

RESULTS

Electrophoretic Composition of Extracts at pH 8.6.—Table II summarizes the findings for six preparations of the 1952 pollen and for four of the 1954 crop. With the exception of the 360-minute, supplementary studies done on the positively charged materials of the 1952 extracts, all analyses were instituted with half-way compensation of the starting boundaries. Because the peaks were usually sharper and more numerous in the ascending than in the descending patterns, the former have been selected for the composite table. In consequence, the mobility and area measurements pertain to the cathodal patterns in the case of the positively charged components whereas they stem from the anodal patterns in the case of the negatively charged constituents. The figures for the major, essentially uncharged peak have been arbitrarily taken from the cathodal limb's photographs. (Inasmuch as the area measurements of this peak differed slightly for the two limbs, the cumulative figure for a given extract does not always amount to exactly 100 per cent in the composite table.)

The several extracts have been listed according to their final pH, which ranged from 6.2 to 4.3. It will be noted that the corresponding values for the extracting solutions ranged from pH 8.4 to pH 3. With one exception, all the extracts of the 1952 pollen possessed the same constituents. They each exhibited, for example, components that migrated at $+2.6$ and at $+1.8 \times 10^{-5}$ cm./sec./v./cm., labeled R-1 and R-2. They also contained five components of negative charge (R-4, R-6, R-7, R-8 and R-9). The component R-5 was encountered, however, only in the instance of the

TABLE III. ELECTROPHORETIC ANALYSES IN ACETATE BUFFER AT pH 5.5, IONIC STRENGTH 0.1 UNDER CONDITIONS OF HALF-WAY COMPENSATION

[illegible]

LOW RAGWEED EXTRACT—LOVELESS AND WRIGHT

glycine HCl extract. If this small amount of negatively charged material was present in the other extracts, it failed for some reason to be resolved. It had also been restricted to the glycine HCl preparation of the 1952 pollen when the six types of extract were examined a year earlier, follow-

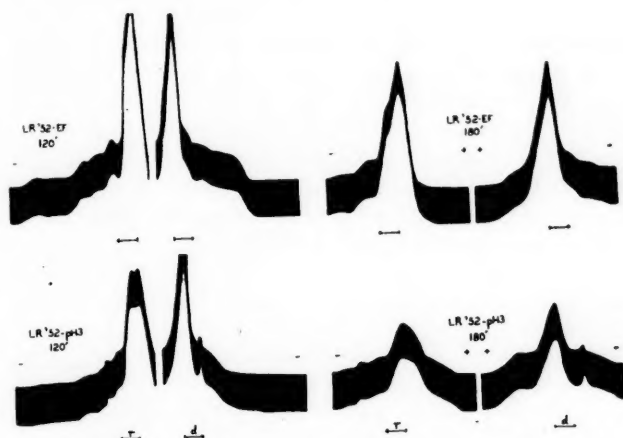


Fig. 1. Patterns provided by two extracts of 1952 pollen. Left-hand set with conventional compensation, righthand set with half-way compensation. Both in barbital buffer at pH 8.6, ionic strength 0.1.

ing conventional compensation of the starting boundaries. (These studies provided area and mobility data that were consistent with those of Table II, despite the lesser age of the defatted, desiccated pollen granules.)

Whereas the mobilities established for the nine components varied little from one extract to another, there was a tendency for the area measurements to shift with the pH chosen for extraction. As is apparent in Table II, the contribution of positively charged components to the overall area of the cathodal patterns increased slightly as the extractant's pH was lower, there being a suggestion of a compensatory influence on the negatively charged components. Meantime, the area occupied by the major peak showed no significant variation, allowance having sometimes to be made for incomplete resolution.

Comparison of these findings for the 1952 pollen with the corresponding results for the several 1954 preparations suggests at first glance, as the lower portion of Table II will indicate, that the latter may have been less complex. Closer examination indicates, however, that incomplete resolution may have accounted for the difference in the two sets of patterns. On this basis, the failure of R-1 and of R-9 to be detected was consistent with the slightly greater areas and mobilities of the components, R-2 and R-8. Such disparities between the 1952 and the 1954 patterns could possibly have originated in the shorter periods of analysis of the latter, albeit

LOW RAGWEED EXTRACT—LOVELESS AND WRIGHT

this variable was at least partially compensated by the slightly higher field strength. It was unfortunate that no examination was made of the glycine HCl preparation of the 1954 pollen. Even if its extra component of negative charge, R-5, had again been detected, however, later cross-tests would have forced us to conclude that it lacked activity as an allergen for VON serum.

In general, therefore, with the possible exception of the glycine HCl extract, all preparations of either pollen crop were essentially alike in electrophoretic composition at pH 8.6, aside from the fact that there were small quantitative changes in the area measurements as the pH of the extractant was shifted.

Figure 1 gives two examples of the patterns. It will be noted that the rising, r, patterns are sharper and more highly resolved than are the descending, d, configurations.

Electrophoretic Composition of Extracts Examined at pH 5.5.—Table III presents mobility data and area measurements for five extracts of the 1952 crop and for three preparations of the 1954 pollen. It is apparent that materials bearing positive charge were resolved into two boundaries as they migrated upward into the buffer toward the cathode, whereas only one boundary appeared during their slower movement downward into the original sample on the anodal side of the cell. The situation was analogous for negatively charged substances (in the opposite arms). As anticipated, positively charged components proved to be more highly charged and mobile than during their examination at pH 8.6, while the converse was true for materials of negative charge. Instead of moving at about -10 , for example, the most highly charged constituent now moved at about -8 . Not only did R-8, R-7 and an adjacent peak containing R-6 and R-5 rise more slowly than they had at pH 8.6, but R-4 was not detected, presumably because its mobility was now so slight that it contributed to the major, essentially stationary peak, R-3.

The number of boundaries resolved from the several preparations was, with a few possible exceptions, the same for the two batches of pollen. One of these exceptions was associated with the analysis of the acetate buffer extraction of the 1954 crop, which exhibited in its cathodal pattern a component of low negative charge that did not appear in any other examination under the same circumstances. Presumably the peak was comprised of the components, R-5, 6, and 7, that had become separated during the analyses at pH 8.6. Since, in the present examination, there was a much smaller R-8 plus R-9 peak than in the case of any other extract, it is permissible to assume that this peak was the source of the extra boundary. In other words, the same materials presumably existed in the other extracts but did not appear as a separate boundary, remaining instead with the rest of the mobile substances of negative charge as they moved down in the cathodal limb. A similar explanation would apply to extra

boundaries encountered in the anodal limb at pH 5.5. One such peak was associated with the first extract of the 1952 pollen as well as with the eighteen-hour water extract of the other pollen. The extra peak, presumed to contain R-5 and R-6, was probably resolved from the major peak ad-

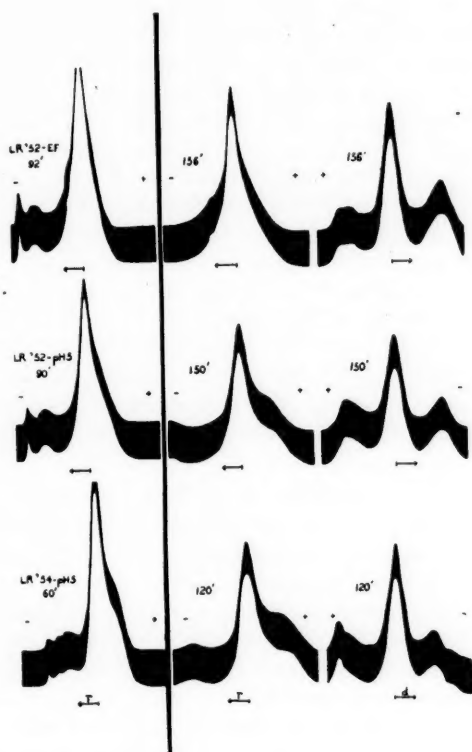


Fig. 2. Patterns provided by two extracts of 1952 pollen, and one extract of 1954 pollen. Both with half-way compensation, in acetate buffer at pH 5.5, ionic strength 0.1.

jacent to it, inasmuch as the latter's area appeared smaller than its counterpart in several other extracts. Similarly, an extra boundary designated R-7 in the acetate extract of the 1954 crop may have separated from the adjacent R-8 peak whose area was inordinately small.

Since none of the extra boundaries appeared in the corresponding preparation of the other pollen crop, it is unlikely that their presence could have been related to the pH of the extractant applied to the granules. It seems more likely that the disparities rested on interactions or dissociations occurring in the complex mixtures, or upon dissimilar degrees of resolution.

The areas of the positively charged components tended, as at pH 8.6, to be larger as the pH of the extractant was lower. Unfortunately, the glycine HCl preparations precipitated so strongly during their equilibration with acetate buffer that electrophoretic analysis was abandoned. Presumably, their positively charged materials would have exhibited the largest areas of any of the extracts.

Figure 2 gives examples of the photographic patterns obtained with several of the extracts during their examination at pH 5.5. The lefthand pattern of each triad was photographed after sixty or ninety minutes of analysis and shows the negatively charged components migrating up into the buffer toward the anode. The two remaining patterns reveal the stage of resolution that had been reached in both the anodal and the cathodal limbs of the cell after an additional hour of electrophoresis.

The foregoing mobility and area measurements were consistent with those yielded by analyses done about a year earlier, under conditions of conventional compensation, on six analogous preparations of the 1952 pollen, indicating stability of the dry granules during storage at R.T.

The combined results of all these electrophoretic studies suggested that the pH of the extractant had little or no influence on the number of constituents of different charge that were withdrawn from the granules, whereas it did affect the relative proportion of positively charged materials extracted.

Immunologic Comparisons Among the Various Extracts.—Table IV is based on challenge tests carried out the day after normal skin had been prepared with mixtures of sensitizing serum and an excess of one or another of the 1952 extracts. It will be noted that the column that had received serum admixed with the alkaline extracting fluid product of extraction responded to none of the challenges with .02 ml of 160-units/ml. Meanwhile, concurrent tests carried out in the control, serum-saline prepared areas with the same testing solutions evinced the desired three-plus reactions, whereas unprepared skin was unaffected by the same solutions. These results indicated that the extract mixed with the sensitizing serum on the preceding day had exhausted the sensitized area's capacity to respond, not only to the same extract, but to all others as well. In other words, the neutralizing extract was a complex antigenic mixture which exhibited all the activities displayed by the other preparations. The next two extracts employed to desensitize the standard sites appeared to be equally complex. Indeed, since all the cross-tests among the three provided negative results, they must have been identical in allergenic composition. When, however, the ten-minute distilled water preparation was selected for the original mixture, only the self-antigen and the two most acid extracts evoked negative challenge responses in row four. The first three preparations, on the other hand, now provoked partial wheal-and-flare reactions, indicating they carried certain activity which was

LOW RAGWEED EXTRACT—LOVELESS AND WRIGHT

TABLE IV. SHOWING ANTIGENIC RELATIONS AMONG SIX PREPARATIONS OF 1952 RAGWEED POLLEN OBTAINED WITH EXTRACTANTS OF DIFFERENT pH Responses of Skin, Sensitized with VON Reaginic Serum and One or Other of Extracts, to Challenge at Twenty-Four Hours with Each of the Other Extracts (.02 ml of 160 units/ml.)

Low Ragweed Extract with which VON Serum was Mixed	Alkaline Extracting Fluid Extract pH 6.2	Phosphate Buffer Extract pH 6.0	Water for 18 Hours Extract pH 5.8	Water for 10 Mins. Extract pH 5.8	Acetate Buffer Extract pH 5.4	Glycine HCl Buffer Extract pH 4.3	Row
Alkaline extracting fluid Extract pH 6.2 2500-unit	0 Self site	0	0	0	0	0	1
Phosphate buffer Extract pH 6.0 1000-unit	0	0 Self site	0	0	0	0	2
Water for 18 hours Extract pH 5.8 2500-unit	0	0	0 Self site	0	0	0	3
Water for 10 minutes Extract pH 5.8 1000-unit	2-	1½	1½	0 Self site	0	0	4
Acetate buffer Extract pH 5.4 2500-unit	1½	2-	2½	2½	0 Self site	0	5
Glycine HCl buffer Extract pH 4.3 2500-unit	2½	3-	2½	2½	2½	0 Self site	6
VON reagin-diluent mixture Unprepared skin	3 0	3- 0	3- 0	3 0	3 0	3 0	7

absent or negligible in the neutralizing extract. When the acetate extract was cross-tested in this manner, only its self-site and that challenged with the glycine HCl extract remained unresponsive, the reactions in all other areas being over half the size of those evoked by the same solutions in the control sites. The final set of challenges, made in areas that had received serum and glycine extract, elicited reactions of nearly maximal dimensions in all but the self-site.

These cross-test results suggest that the more acid the extractant, the less complex in general is the extract. More strictly speaking, maximal complexity resulted from the eighteen-hour application of extractants of pH 8.4, 7.5, and about 7 to the granules. When, however, distilled water at about pH 7 was restricted to a ten-minute contact, a more simple product resulted. Still greater simplification was achieved by using acetate buffer at pH 5 as the solvent for eighteen-hour extraction, while the fewest activities were taken from the granules by the glycine HCl buffer of pH 3. This anionic-cationic mixture is probably complex antigenically.

Re-examination of the cross-test results of Table IV in a vertical manner permits the conclusion that no fewer than four allergens, or groups of allergens, exist in low ragweed pollen. One of these appeared in the simplest extract, a potent solution derived from glycine HCl extraction. A second must have been present in the acetate buffer product, since it evoked a decided challenge response in a site that had been desensitized with the simpler preparation. Meantime, the reciprocal test was ineffectual, showing that the acetate extract exhibited all the activity carried by the glycine extract. The former, therefore, contained at

least two active entities or groups. A similar relationship existed between the acetate buffer product and the flash extraction carried out with distilled water. Whereas, therefore, the distilled water removed from the pollen all the activities that characterized the acetate buffer extract, it also withdrew some additional allergen which enabled it to light up a site that was unable to respond to the homologous acetate extract. Thus, a third activity is accounted for. Evidence for the fourth is to be found in the challenge response elicited by the eighteen-hour water extract in a site that had been desensitized with the flash preparation. It was duplicated by each of the two remaining extracts.

For some reason, the acetate extract of the 1954 pollen was more complex than its 1952 counterpart. Indeed, according to cross-tests, it possessed all the activities of the most complex 1952 extracts. The two crops must, therefore, have been identical in antigenic constitution.

DISCUSSION

Although this study was inspired by the likelihood that both the allergic activity and the electrophoretic composition of ragweed pollen extracts might be influenced by the pH chosen for extraction, only the former assumption was substantiated. Indeed, little or no difference could be detected in the number of electrophoretic components yielded to the solvents when their pH values varied from 8.4 to 3. (There were a few instances, nonetheless, where an extra peak was encountered. The slightly altered mobilities and area measurements of an adjacent component suggested, however, that electrophoretic resolution had been more advanced than usual in all but one of these sporadic exceptions.) On the other hand, the amount of material of positive charge seemed to be greater as the pH of the pollen solvent was lowered. Could the latter finding be related in any way to the increasingly simpler antigenic character of these extracts?

Obviously, a mere increase in the amount of positively charged material without an associated decrease in the number of components could not account for antigenic simplification. Since, however, there was a concomitant tendency for the negatively charged constituents in the extracts to appear in lower concentration, there is a remote theoretical possibility that the extractant's pH did contribute to the immunological findings. The basis for this contention is the fact that there is a lower limit to the amount of allergen that can be detected by any biologic method. If, therefore, the concentration of negatively charged materials were to drop in successive extracts to a level where one after another of them escaped immunologic detection despite their continued presence in the electrophoretic patterns, evidence of antigenic simplification would not be accompanied by electrophoretic simplification. Indeed, in the case of the highly simplified glycine extract, the electrophoretic pattern revealed the existence of an extra peak of intermediate negative charge at pH

8.6. Hence, the most simplified product by activity test gave the appearance of being the most complex from the electrophoretic viewpoint. One could not, at any rate, predict the allergenic nature of the various preparations from their electrophoretic compositions, with the possible exception of the glycine HCl extract—whose pH 8.6 patterns require confirmation and whose extra component, R-5, appeared to exist in other extracts when they were examined at pH 5.5.

Despite our disappointment in this regard, the outcome of these experiments should facilitate future investigations, especially those concerned with the electrophoretic (or electro-convective¹¹) isolation and characterization of allergens in pollen. It will be a boon, with so complex a chemical, electrophoretic and antigenic mixture as pollen extract, to start off with a preparation that has been antigenically simplified with the gentle procedure of selective extraction only. In the case of the glycine HCl extraction, for instance, at least three antigens or groups of antigens related to human allergy either will be missing or present in undetectable amounts. At the same time, the extract will be relatively enriched in the positively charged components, R-1 and R-2. At least the first of these will exhibit activity with appropriate reaginic serum and in rather low concentrations, as little as .002 mg N./ml sufficing to light up a sensitized area in normal skin, according to Loveless and Timasheff.⁷

If, on the other hand, the investigator is more concerned with the pigmented constituents, there would be a somewhat higher concentration of these antigens in alkaline extractions of the granules. Several of the pigments are known to be active in man, Abramson's group⁸ having tested the fastest moving ones for potency in allergic skin, while Loveless et al⁶ used the cross-neutralization procedure of passive transfer to demonstrate the individual specificities of three of these pigments that had been separated by chromatography.

Even if attention continues to be focused on the so-called immobile "component," interpretation of fractionation results will be simplified by controlling the extractant's pH, since the composition of this component will vary with the pH selected for its isolation. (See Becker's² Fig. 6 for the pH mobility curves and iso-electric points of five antigens in low ragweed.) In addition to such immobilized constituents, it is likely that the major component contains other uncharged material which remains stationary at all pH levels and which may or may not account for the biologic activity of immobile fractions prepared by various investigators^{9-12,13} under different conditions. Indeed, one group¹² has speculated that ragweed allergy in man may depend on a "master antigen" that presumably exists either in the free state or in combination with numerous carrier substances. Despite the appeal of this hypothesis, it stems from gel diffusion studies which reveal^{12,13} that ragweed pollen is comprised of multiple antigens for the rabbit, and has been explored in allergic man only by cutaneous tests¹² that appraise the relative potencies of pollen

fractions. It is hoped that the proponents of this theory will examine the relative *specificities* of their fractions by the cross-neutralization procedure described in the present report or by some comparable absorption technique for human serum reagins. Such evidence to date^{6,7,14} indicates that man responds to multiple allergens in ragweed pollen. This is consistent with the present report, which proposes no fewer than four antigens.

It should be remarked in closing that the actual composition of low ragweed extracts may be less complex than the electrophoretic patterns imply. Indeed, with both negatively and positively charged constituents present at all pH levels, interactions between the oppositely charged molecules are always possible. Such interactions and dissociations would tend to alter the charges and thereby change both the mobilities and the area measurements. Indeed, they may account for the differences noted in the patterns of the two limbs of the U-tube. As a matter of fact, complications of this nature are at times encountered even when mixtures of proteins bearing the same sign are under analysis. It is indispensable, therefore, to employ additional criteria when such complex preparations as pollen extracts are being characterized.

SUMMARY AND CONCLUSIONS

1. A series of extracts has been prepared from two crops of low ragweed pollen by exposing the granules to extractants of graduated pH for eighteen hours (in one instance, for only ten minutes). Each was characterized by cross-tests in normal skin that had been prepared with human reaginic serum, and by moving boundary electrophoresis at pH 8.6 and at pH 5.5.

2. With the possible exception of a glycine HCl extract which at 8.6 had an extra peak, all extracts possessed the same electrophoretic components. However, as the pH of the extractant was lower, more material of positive charge was withdrawn from the granules. Hence, the extractant's pH exerted a quantitative but not a qualitative effect on the resulting extract.

3. Cross-tests among the 1952 pollen preparations in reagin-prepared human skin revealed a distinct influence of the extractant's pH on the antigenic complexity of the resulting extract. The most acidic preparation was the least complex immunologically. At least one additional allergen was removed by the pH 5 acetate buffer. Still another activity emerged when the granules were exposed to distilled water for ten minutes. Preparations of maximal and identical complexity were procured when water, phosphate buffer at pH 7.5, or alkaline extracting fluid at pH 8.4 was applied to the pollen for eighteen hours. For some reason, a pH 5 acetate buffer extract of the 1954 pollen crop also possessed all the allergens of these complex solutions, thus differing from its 1952 counterpart. This could not have rested on any difference in the allergenic character of the two pollens, since the mutually negative cross-tests established them as being identical. The findings require confirmation.

LOW RAGWEED EXTRACT—LOVELESS AND WRIGHT

4. Regardless of the demonstrated differences in their allergenic complexity, the various extracts carried roughly the same activity per protein N unit in Prausnitz-Küstner tests. Furthermore, their allergenic composition could not be predicted from their electrophoretic patterns (with the possible exception of the glycine HCl extract).

5. No convincing evidence was found for an innate difference between the two pollen crops, occasional deviations in the electrophoretic patterns being tentatively attributed to unequal resolution in the paired extracts. The same mixture of allergens existed in both pollens.

6. Low ragweed pollen is electrochemically and antigenically heterogeneous, containing no fewer than four antigens of different specificity for man.

7. A gentle means of procuring antigenically simplified extracts is to apply extractants of low pH to the pollen granules.

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409

CORRECTIVE BREATHING EXERCISES FOR PATIENTS WITH BRONCHIAL ASTHMA AND OBSTRUCTIVE PULMONARY EMPHYSEMA

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THE IMPORTANCE of corrective breathing exercises in management of patients suffering from bronchial asthma and obstructive pulmonary emphysema should not be underestimated. Standardization of technique with strict adherence to physiologic principle can lead to universal acceptance of breathing exercises in clinical therapeutic procedure.

In the above-named diseases, there is obstruction of the bronchial passageways that produces air trapping and overinflation of the lungs. In addition, lung tissues are damaged and exchange of oxygen and carbon dioxide at the physiologic level is diminished. This paper is limited to application of corrective breathing exercises as they pertain to the ventilatory system where obstruction to airflow occurs.

There are many reasons why breathing exercises, with the patient lying flat, are efficacious. With the body erect, the descent of the diaphragm is aided by downward gravity pull from the weight of the abdominal organs. The same force opposes upward movement of the diaphragm during expiration. With the body in a supine position, it is different. In this position, the direction of force exerted by the abdominal organs is opposite in the respiratory cycle to the direction of force with the body in an erect position. That is to say, the force operates to keep the diaphragm elevated and lung volume reduced rather than increased. Furthermore, the inward weight of the chest wall in the supine position helps to reduce lung volume which in effect opposes air-trapping or overinflation.

Elevation of the diaphragm accompanying reduction of lung volume allows wider excursion of the diaphragm with resulting increased distribution and diffusion of air in the lungs. Lying flat, the patient is less likely to become fatigued or to develop excess accumulation of carbon dioxide in the lungs. Moreover, because some patients are confined to bed, it becomes a necessity, from the clinical standpoint, to understand the technique of conducting corrective breathing exercises with the patient lying flat.

To improve ventilation of the lungs by corrective breathing exercises, patients must be taught how to apply and regulate force during expiration.

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CORRECTIVE BREATHING EXERCISES—WALSH

Loss of elasticity of lung structure lessens the rate of exchange of oxygen and carbon dioxide as a result of excess accumulation and stagnation of air in the outer regions of the lung where blood flow is greatest. Breathing difficulty is further increased in elderly patients because, in old age, asthma and emphysema usually occur together. In the late stages of the latter disease, after the lungs are permanently expanded, obstruction to air flow may become minimal but respiration remains markedly impaired because ventilation is not sufficient to compensate for the increased lung volume.

At the beginning of the training program, the patient is taught how to fill and empty his lungs so that he can lessen the number of attacks of shortness of breath and shorten their duration. The necessity of emptying his lungs of at least as much air as he breathes in should be emphasized.

In determining the length of exercise periods, consideration should be given to the patient's age, size, and physical and mental conditioning. Ordinarily, the exercises last five minutes or more on morning awakening, evening retiring, during noon rest period, and at the onset of and during attacks of shortness of breath.

Interest and co-operation may be gained by telling the patient that the tissue lining of the air sacs or alveoli of the lungs has a surface area twenty-five times greater than the body skin area, and that in average resting respiration the alveolar tissues are in contact with approximately six thousand quarts of air and seven thousand quarts of blood in transit through the lungs daily. It will be further advantageous for the patient to know that elaborate physiologic studies of the interaction of the lungs and heart have been performed in the laboratory. These studies have shown that even during mild exercise, because of increased circulation of air and blood through the lungs, the oxygen uptake per unit of time may increase to twelve times that taken into the blood under resting conditions.

After the patient has been psychologically conditioned, his training may begin. A pillow is placed under his head and shoulders. This will raise the head and shoulders slightly above the base of the chest, allowing transmission of greater proportion of chest wall inward force toward the lung base where it can be most effective. A pillow is likewise placed under the knees to raise them slightly above the body trunk and to relax both abdomen and chest. In turn, better excursion of abdominal wall musculature and diaphragm follows. Breathing both in and out should be through the nose. The palms of the hands are held against the lowermost ribs with the elbows pointing outward and resting flat. Inspiration is brisk and short and largely dependent upon quickened contraction of the diaphragm. Expiration is prolonged to avoid raising the pressure of trapped air in the alveoli to an extent that will exert check-valve-like action upon the bronchi and further obstruct emptying of the lungs. This will require practiced control on the part of the patient. Near the very

CORRECTIVE BREATHING EXERCISES—WALSH

end of expiration the abdominal muscles are gradually tightened and increasing external pressure is applied by the hands, squeezing both sides of the base of the chest together.

If force is controlled and the exercise is done exactly in the above manner, it will not be necessary to instruct the patient to create back pressure in the lungs by pursing his lips, whistling, hissing, or grunting during expiration, in order to offset possible bronchial obstruction resulting from any check-valve-like action.

A separate exercise is given to enable the patient to gain control of and strengthen the diaphragm by having him breathe with a five-pound sand bag placed upon the abdomen. The action of the abdomen, in lifting the sand bag by each inspiration, imposes extra work on the diaphragm. Except for the latter exercise, the training program outlined may be done if need be, with the patient standing or sitting.

The techniques of the foregoing breathing exercises are particularly appealing because of their simplicity and efficiency in contributing to restoration of normal breathing mechanics. This in turn conditions patients for better exchange of oxygen and carbon dioxide in the lungs and for adjustment to increased physical activity and oxygen requirements.

Results of correlated data showing clinical improvement of patients, permit one to conclude, especially in respect to rehabilitation, that a program of corrective breathing exercises is an important feature of management. If nothing more, through understanding, the patient's fear is lessened and he is able to feel he is no longer entirely dependent upon drugs for relief, but rather that he has been shown an entirely practical method with which to combat his lung disability throughout his lifetime.

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ALLERGY TO PROTEINS DERIVED FROM ANIMAL SOURCES AS SEEN IN IMMUNIZATION PROCEDURES

Effective Substitute Measures

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WITH the recognition of allergy as a vital part of medical practice, more and more attention is being paid by the profession to the prevention of hypersensitivity reactions to therapeutic procedures. Thanks to present immunization methods, many infectious diseases have been eliminated. However, the injection of protein materials from varying animal sources has caused a proportionate increase in severe and fatal reactions to these species-specific antigens.

The purpose of this paper is to familiarize the practicing physician with modern immunizing procedures and their hazards. We shall attempt to suggest available and effective substitute sera and supplemental antibiotic agents, should a patient be sensitive to the commonly used materials.

A state of immunity may be artificially produced by either passive or active immunization. In passive immunization we take advantage of any mammalian system to produce antibodies which are injected in order that the patient may quickly augment his own defenses to bacteria and their toxic products. However, the duration of such protection is short, lasting from a few days to several weeks. In active immunization, attenuated bacteria and their products are injected in order to stimulate the patient's own body defenses to produce the specific antibodies. This procedure should be the one of choice. The established immunity usually lasts for many years. However, it may take several weeks or months before the desired antibody titers can be obtained.

When using immunizing agents containing animal proteins, two chief types of allergic reactions may be encountered:

1. *Serum Accidents, Constitutional Reactions or Anaphylactic Shock.*—These conditions are often explosive in onset and may involve all body tissues. There may be manifestations of extreme fear, dyspnea, cough, asthma, tightness in the chest, abdominal cramps, vomiting, diarrhea, uterine contractions, urticaria, convulsions, deep shock and many others. They may terminate fatally despite heroic measures.

2. *Serum Sickness.*—This reaction appears approximately ten days following the injection of the offending antigen and manifests itself as: fever, skin rashes or urticaria, arthralgia, lymphadenopathy and neurol-

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ALLERGY TO PROTEINS—ZUCKER AND FLORIO

TABLE 1.

Disease	Prophylactic or Therapeutic Sera or Vaccines	Animal Source of Sera or Vaccines	Frequency of Reaction	Substitute Sera or Vaccines	Effective Antibiotics
Tetanus	P, Th.	HORSE SERUM Antitoxin	Very freq.	Bovine antitoxin (Sharp & Dohme)	Penicillin or other antibiotic (with antitoxin)
Diphtheria	P, Th.	Antitoxin	Very freq.	None	Penicillin or other antibiotic (with antitoxin)
Gas gangrene	P, Th.	Antitoxin	Very freq.	None	Penicillin or other antibiotic (with antitoxin)
Snake and black widow spider bites	Th.	Antivenin	Very freq.	None	None
Pertussis	P, Th.	RABBIT Antipertussis serum	Rare	Human anti-pertussis serum (Cutter and Hyland)	Tetracyclines and Chloramphenicol
Rabies	P	Rabbit brain tissue	Rare	Duck egg vaccine or rabbit serum (Lilly) or horse serum (Lederle)	None
Poliomyelitis	P	MONKEY TISSUE Monkey kidney	Very rare	Gamma globulin	None
Influenza	P	CHICK EMBRYO Allantoic fluid	Freq.—rare	None	None
Mumps	P	Periembryonic fluid	Freq.—rare	Human hyperimmune serum (Hyland)	None
Equine encephalomyelitis	P	Chick embryo protein	Freq.—rare	None	None
Yellow Fever	P	Chick embryo protein (U. S. Publ. H. S.)	Freq.—rare	None	None
Rickettsial diseases					
Typhus	P	Yolk sac	Freq.—rare	None	Tetracyclines and Chloramphenicol
Q fever	P	Yolk sac	Freq.—rare	None	Tetracyclines and Chloramphenicol
Rocky mountain spotted fever	P	Yolk sac and chorioallantoic membrane	Freq.—rare	None	Tetracyclines and Chloramphenicol

ogical manifestations (especially following tetanus antitoxin). With the use of present therapeutic agents such as epinephrine, corticosteroids and antihistamines, prognosis is usually good.

All efforts have to be made to anticipate and prevent the occurrence of allergic reactions. A detailed history should be taken in order to detect any allergic family predisposition, as well as past allergic manifestations of the patient. Gastrointestinal disturbances after ingestion of foods (especially eggs) and pulmonary symptoms after exposure to horse dander should be investigated. Patients, however, are often ignorant or forgetful about the type of injections they have received. If evidence of past sensitivity to animal proteins is found, skin tests with much greater dilutions than ordinarily used must be done and testing with horse serum or egg proteins should be started with dilutions of 1:1000.

Passive transfer tests are more difficult and time consuming, but are

indicated whenever severe reactions are anticipated. Since scratch tests are much safer, many allergists use this method prior to intradermal testing. The ophthalmic test in accordingly low dilutions gives reliable and safe information of the patient's state of sensitivity.

Constitutional reactions following skin tests, or a history of severe reactions to these protein injections, should definitely be considered a contraindication to their use. In rare circumstances, when no substitute sera or effective antibiotic agents are available (see tabulation), and if the course of the infection would otherwise terminate fatally, the calculated risk of using these substances in highly allergic patients may be considered. They should never be used intravenously in these cases. The patient should be hospitalized and his family informed of the circumstance.

It is sometimes difficult to find veins in normal persons, especially in children and infants, and certainly almost impossible during shock with collapse of peripheral circulation. Since many anti-anaphylactic drugs are highly effective when used intravenously, and since an infusion of 5 per cent glucose in saline is a valuable aid in combating shock, it may prove to be of great advantage to start the infusion prior to administering the immunizing material if a dangerous reaction is expected.

The influence of ACTH or cortisone on antibodies is still under debate, but no definite evidence of their inhibitory effect in man has been found.¹ We feel that it might be advisable to initiate treatment with one of these drugs before beginning immunizing procedures in allergic patients. They may be continued throughout and after the course of injection treatment. Keeney et al.² were able to use this method in two patients who had previously experienced anaphylactic reactions to tetanus antitoxin.

Excellent results with marked decrease of allergic side effects have been obtained by combining antihistamines with penicillin, iodine-containing contrast media for intravenous urography³ and blood transfusions.⁴ Brenner,⁵ in a patient suffering from subacute endocarditis, and highly sensitive to penicillin, succeeded in administering large doses of the drug by using ACTH and Chlor-Trimeton.

Injections of sera should be given in the arm so that a tourniquet may be placed proximal to the site of injection, in order to prevent rapid distribution of the antigenic material through the system, should signs of sensitivity be encountered.

A full dose of serum should never be given to patients allergic to the specific material, but multiple-dose rapid desensitization in conjunction with one of the previously mentioned drugs could be tried. It is advisable to start with 0.1 cc of the lowest dilution (subcutaneously) to which the patient does not show any positive reaction. The material should then be given every fifteen to thirty minutes in gradually increasing doses until the concentrated serum can be administered by intramuscular route.

Treatment of a constitutional reaction must be instituted promptly; epinephrine being the drug of choice. Up to 0.5 cc of this drug should be

ALLERGY TO PROTEINS—ZUCKER AND FLORIO

given above the injection site and a similar dose in the other arm. This procedure might have to be repeated several times. Other helpful drugs are antihistamines, aminophyllin and corticosteroids. Infusions of 5 per cent glucose in saline with levophed or neosynephrine are an excellent procedure to combat shock, with the rate of flow adjusted according to the blood pressure readings. Oxygen inhalations with mechanical respiration may be indicated.

We are primarily concerned with immunizing procedures and concurrent species-specific allergies to proteins derived from the following animal sources:

HORSE SERUM

Since the horse has the ability to produce large amounts of antitoxins, the sera against diphtheria, tetanus, gas gangrene, and antivenins are usually derived from this source. Skin tests with horse serum are not always reliable. Constitutional reactions have occurred in patients giving negative skin tests, and patients with positive skin tests have occasionally tolerated injections of horse serum.

Skin reactions may persist for as long as twenty-five years after administration of equine sera. Asthmatic patients who are sensitive to horses sometimes react to both horse sera and horse dander, as demonstrated by Ratner.⁶

Tuft and Heck⁷ state that "A positive skin test to horse serum constitutes definite indication of previous sensitization by horse serum which could not be acquired any other way except by previous antigen contact, usually artificially induced."

Up to 90 per cent of patients become sensitized to equine serum if large doses are used. Although the antigenic property of antitoxins is reduced by concentration and heating, they are still highly allergenic materials.

Horse sera containing biologicals are used for passive immunization against:

1. *Diphtheria*.—In this disease the serum primarily is used therapeutically. The antitoxin has to be administered as early as possible, and in amounts large enough to inactivate all of the circulating diphtheria toxin. It will not affect any toxin already bound to the tissues (primarily nerve and myocardial cells). It has no bacteriolytic effect on the diphtheria bacillus itself, and additional antibiotics for bactericidal effects should be given. Penicillin is approximately 75 per cent effective in eradicating diphtheria organisms from the nasopharynx. In cases of penicillin allergy, or if the diphtheria bacillus is resistant to this drug, other broad spectrum antibiotics may be indicated. It is also advisable to give diphtheria toxoid starting one week after the illness.

With the introduction of active immunization against diphtheria, the incidence of this disease has greatly declined. The U. S. Public Health

Service Reports list 150,000 cases from forty-one states in 1920, and only 2,355 cases from all states in 1953. The use of antitoxin and their concomitant reactions have naturally declined in proportion.

Diphtheria toxoid is obtained from the toxin by removing its toxic effects without influencing its immunizing qualities. It does not contain animal proteins. Reactions to toxoids are probably due to formalin. Sensitivity to the diphtheria bacillus proteins can be demonstrated by Schick-control test (heated diphtheria toxin) and Moloney test (diluted diphtheria toxoid). They are frequently positive in older children and adults, and should be done prior to toxoid administration in these age groups. In the past, repeated exposures to diphtheria continued to immunize adults against this disease. The susceptibility of our adult population, however, has increased with the decline of this stimulus.⁸ In the first half of 1956, nearly 20 per cent more diphtheria cases have been reported in the U. S. as compared to the same period in 1955. This fact certainly indicates the need for more complete immunization of our population. More extensive skin tests, especially of older children, should be done to detect those with low antibody titers. Adults professionally exposed to diphtheria should also take advantage of these prophylactic measures. Frequently, only small amounts of toxoid are needed to boost existing antibody titers.

2. *Tetanus*.—Tetanus toxin is one of the most powerful poisons known with a high specific affinity for nerve tissues. The antitoxin is usually derived from equine sources and carries the same risks of allergic manifestations as the diphtheria antitoxin. Tetanus antitoxin is used as a prophylactic passive immunization and should be given for any wounds or burns suspected of being contaminated with clostridium tetani. Injections may have to be repeated at weekly intervals, since protection only lasts about one week to ten days. For this reason, large initial doses, up to 10,000 units, have been generally adopted, especially if there has been some delay in administering the antitoxin. This method will provide longer lasting protection and may eliminate the risk of allergic reactions encountered with multiple injections given over several weeks. If the patient had been previously immunized with toxoid, he should also receive a dose of fluid toxoid, using separate syringes. This booster will raise antitoxin levels to a satisfactory titer within approximately one week.

Once the disease is established, much larger doses have to be administered. The injections should be given intramuscularly since the intravenous and intrathecal routes carry a higher incidence of more severe reactions and are therefore rarely advocated. In patients unable to tolerate the equine antitoxin, bovine serum must be used. Tetanus, unlike diphtheria, does not confer lasting immunity, and repeated sub-clinical exposures do not stimulate or increase antibody formation. Emil

von Behring's laboratory assistant sustained three attacks of tetanus from which he recovered.⁹ Penicillin or other antibiotics probably aid in controlling the local tetanus infection and should be given in all cases. However, these drugs will not neutralize the toxin once the disease is established. The mortality of severe tetanus cases is still approximately 50 per cent. From 1948 to 1952, approximately 500 cases were reported annually in the U. S. Our armed forces, however, showed the efficacy of adequate tetanus prophylaxis with repeated toxoid, and indicated only fourteen cases in the Army and Navy during World War II.

It is common practice in the U. S. to start infants on a basic course of triple vaccine (DTP) and give boosters thereafter. However, our adult population, especially those in hazardous industries who are prone to injuries, is definitely neglected as far as tetanus prophylaxis is concerned. These people should receive a basic immunization course of tetanus toxoid, if not previously administered, with boosters every three to four years. Subsequently, in case of injury, a single injection of toxoid is sufficient. Satisfactory antibody titers have been found after ten years or more.¹⁰

Members of our armed forces have an individual immunization record which is sent along whenever they are transferred. A similar system might be effective in private practice with the physician keeping one copy in a dated filing system which enables him to recall any delinquent patient for a needed booster dose.

Adequate tetanus prophylaxis with toxoid would prevent a great part of our population from being sensitized to horse serum.

3. *Gas Gangrene*.—Gas gangrene is caused by different organisms of the clostridium genus, of which the tetanus bacillus is a member. The infection usually occurs in contaminated wounds with extensive tissue damage.

Specific exotoxin is produced by each organism of this group and commonly used antitoxins must therefore be polyvalent in order to be effective. They are usually administered in combination with tetanus antitoxin as a prophylactic or therapeutic measure. Gas gangrene toxoid has been produced but has not been found effective. Antibiotics should also be administered.

4. *Antivenin*.—Snake bites may cause the entry of powerful toxins into the human body. Hyperimmune equine serum against the venoms of the pit viper (*Nearctic crotalidae*) is available. A horse serum containing antivenin against black widow spider poisons (*Latrodectus mactans*) is also produced. Both sera are used therapeutically.

RABBIT PROTEIN

Although sensitivities to rabbit protein are not as common as to horse serum, precautions against reactions are obligatory. With the intra-

muscular use of this material (antipertussis serum), Kaplan and Larsen¹¹ did not encounter any sensitivities. Ceresko and Raskin¹² skin tested 110 patients and failed to obtain a positive reaction, and no allergic manifestations occurred after the injections.

However, with the intravenous use of rabbit serum (anti-*Hemophilus influenzae*), frequent reactions were encountered. Smith and Wilson¹³ reported that twelve out of twenty-seven patients treated had "side reactions," two of which were of the severe anaphylactic type. All their patients had ophthalmic tests performed. Ross et al¹⁴ estimated delayed serum reactions in approximately 20 per cent of patients treated with this serum.

The production of anti-*H. influenza*, type B, rabbit serum has been recently discontinued, since the newer antibiotics have been found to be highly efficacious as therapeutic and prophylactic agents. This serum,¹⁵ like the anti-pneumococcus horse serum, is now of historic interest only.

1. *Pertussis*.—Whooping cough continues to cause a high mortality among children, especially infants under one year of age. Fifty to seventy per cent of all deaths from this disease occur during this period. One attack usually confers permanent immunity. It has been suggested that "bacterial asthma" may be a sequel to acute infectious diseases like pertussis.

Prophylactic vaccine inoculations will protect a large percentage of children, and, if the disease occurs, it will be much milder and complications less frequent. Encephalopathy has occurred after the administration of pertussis vaccine. The cause of this reaction is unknown, and great care should be taken in giving the vaccine to children with a history of central nervous system disease.

Passive immunization is indicated in exposed susceptible infants and debilitated children, and in the treatment of the disease itself. Besides the anti-pertussis sera from rabbit sources, highly effective human sera are available, and generally used. The latter have not caused serious local or general reactions, and can safely be given in repeated doses, since there is no danger of sensitizing the patient against human sera *per se*. Fasting donors are used in order to avoid passive transfer of allergens. Broad-spectrum antibiotics are effective.

2. *Rabies*.—This disease is caused by a neurotropic virus, and death is inevitable once symptoms have developed. Immediate cleansing of the wound is of utmost importance. Semple vaccine, which is commonly used in the U. S., has decreased the mortality of persons bitten by rabid animals from about 20 per cent to 0.25 per cent. Active immunization during the incubation period (ten days up to seven or more months) is attempted. The vaccine contains rabbit brain tissue, and allergic local reactions or urticaria are rarely encountered. Encephalomyelitis and

ALLERGY TO PROTEINS—ZUCKER AND FLORIO

paralysis, which often terminate fatally, are caused by organ specific allergy to the brain tissue. This complication has been reported to occur in about one in 2,000 to one in 7,000 persons treated. The vaccine should be stopped at the first sign of central nervous system involvement. Sometimes the differential diagnosis between the allergic type of paralysis and manifestations of rabies itself might be very difficult. However, once the disease is established, further treatment is of no value.

A serum from equine sources is available for passive immunization and is effective when given within seventy-two hours after exposure. This serum is valuable in infections with a short incubation period. In the absence of allergy to horse serum, it may be administered under certain circumstances: (1) In cases of previous rabies vaccine administration (vaccine immunity lasts only for several months); (2) while waiting for reports regarding the condition of the animal which inflicted the bite; (3) in conjunction with vaccine in serious injuries (especially around the head and neck); and (4) if treatment with vaccine has been delayed. A similar antiserum manufactured in rabbits is available as a service item for clinical trial. Details may be found in the *Suggestion of Special Committee on Rabies, World Health Organization, 1953*.

Recently a vaccine, grown on embryonic duck tissue, was made available commercially. However, since patients may be sensitive to this protein, and since there exists a cross sensitivity to chicken egg protein, the same precautions as previously mentioned should be taken. Localized or general reactions may be experienced. This vaccine is not prepared from nerve tissue and contains little or none of the paralytic factor;¹⁶ it may be indicated if a second series of inoculations is required. Substitution of this vaccine may reduce or completely eliminate central nervous system complications.

Animal bites frequently carry the risk of tetanus infection, and antitoxin or toxoid may also be required.

MONKEY TISSUE

Poliomyelitis vaccine is prepared by cultivating representative strains of the three types of poliomyelitis virus in monkey kidney tissue culture, bathed in a synthetic nutrient medium. The incidence of local and systemic reactions is extremely low.¹⁷ Occasionally there may be local soreness and erythema which may last for twenty-four to thirty-six hours. Fever and malaise and general urticaria have been reported, but no serious reactions such as anaphylaxis have been encountered. Sensitivity may be due to antibiotics, preservatives, horse serum, soluble proteins, Rh antigens and other possibly antigenic factors, depending on the choice of the manufacturer. Some of these ingredients are present only in minute amounts in the final product; horse serum less than one part in 5,000,000; penicillin less than 0.003 U/cc. The literature does not reveal any cases of organ specific sensitivity due to injection of kidney tissue.

ALLERGY TO PROTEINS—ZUCKER AND FLORIO

Salk¹⁸ reported that intradermal administration of kidney culture fluid in sixty-four subjects on two or more occasions did not reveal any dermal sensitivity.

The vaccine is of no value if given after the beginning of the incubation period because it takes several weeks for a favorable degree of immune antibody response.

Gamma globulin is the only other alternative measure. But, although gamma globulin has been used in epidemics with effectiveness, the consensus seems to be that it is of limited value in household members. It is approximately 10 per cent effective, because 90 per cent of the cases that occur in household contacts occur so soon after the index case.¹⁹ Nonetheless, it should be used to protect the 10 per cent in whom the incubation period is sufficiently long so that it might be effective.

There is no specific therapy for the established disease.

CHICK EMBRYO

The culture media of choice for the rickettsiae and viruses appear to be chick embryo. Vaccines against these organisms, therefore, contain small amounts of chicken or egg proteins which act as species-specific antigens in allergic individuals. Ratner et al²⁰ state that only 0.5 per cent of the general population and only 5 per cent of allergic persons are sufficiently sensitive to egg to warrant special precautions in the administration of chick embryo-propagated viral and rickettsial vaccines.

Clinical egg allergy seems to be more predominant among allergic infants and children, especially those with eczema. It has been suggested that sensitivities to this protein may start *in utero*. Food allergies decrease with age; and, subsequently, the inhalants become the predominant offenders. Allergy to chicken and to egg proteins often occurs simultaneously. Fortunately, only a small proportion of skin reactors show clinical allergy to these antigens.

A positive skin test indicates either present intolerance or residual clinical sensitivity due to past sensitization, no longer capable of harmful effects. In contrast to horse serum, which is truly a "foreign protein", chicken egg is contained in most of our foods in some form or other. This fact would explain the difference in allergenicity between the two.

Ratner et al²¹ state that the number of patients sensitized following injections of viral and rickettsial vaccine is negligible.

Seal²² quotes that, after 77,000 individual injections of influenza vaccine given to members of the U. S. Armed Forces in the Fall of 1955, only two anaphylactic or severe allergic reactions were observed. Both patients had avoided answering questions about egg allergies.

However, the relative safety of these biologicals does not preclude their extreme danger in egg sensitive patients. The egg protein content of these vaccines may be cut to a minimum by chemical or mechanical

means (precipitation, agglutination, adsorption, centrifugation and others). Sensitivities to preservatives like formalin are also apt to occur in very rare instances. Since these egg propagated vaccines are used as prophylactic measures, the risk of giving them to allergic individuals must be very carefully weighed. One may attempt to give them in repeated small doses several weeks apart, in combination with adrenalin or antihistamines.

Vaccines against the following diseases caused by viruses are prepared from chick embryo.

1. *Influenza*.—This disease generally occurs in epidemics: Groups A and B viruses are usually encountered. The strains differ in immunologic respects, and immunity against one does not protect against the others. Inactivated influenza type A, A', B, and B' strains are contained in some of the so-called polyvalent vaccines. Variations in antigenic properties of groups A and B may account for degrees of effectiveness of the vaccine during different epidemics.

Antibody levels, probably caused by repeated subclinical exposures, may be helpful in determining susceptibility to influenza in older individuals and indicate the need for prophylactic vaccination of allergic persons during epidemics. Immunization gives a declining rate of protection up to six or eight months following vaccine injection. Depending on the groups of organisms (A or B), the incidence of the disease may be 70 per cent to 90 per cent lower in vaccinated persons than in those not vaccinated.²³

2. *Mumps (Epidemic Parotitis)*.—This disease occurs chiefly in children and confers a lasting immunity. Routine prophylactic vaccine injections of children are not advisable, since they may delay the occurrence of mumps until adulthood, when more serious complications are usually encountered.

Dilute mumps vaccine, especially prepared for skin testing, gives a delayed tuberculin-like reaction in persons susceptible to this disease. The egg protein in this material may also cause immediate skin reactions in cases of egg sensitivity. Mumps skin tests are indicated in exposed adults and in children, if specific circumstances make the protection against mumps at any particular time desirable.

Mumps has a fairly long incubation period (eighteen to twenty-one days). The vaccine causes increase in antibody titers within one week after administration, and is therefore a valuable aid if given early during the incubation period.

There seems to be sufficient evidence that gamma globulin prepared from human hyperimmune serum may act as prophylactic immunization, or modify the disease or some of its complications.

None of the antibiotics are effective against mumps virus.

ALLERGY TO PROTEINS—ZUCKER AND FLORIO

3. *Equine Encephalomyelitis*.—Administration of vaccine against this disease is only indicated in persons who are exposed to the virus in the course of their occupation. Treatment is symptomatic.

4. *Yellow Fever*.—This disease has completely disappeared from North America. An effective vaccine is prepared with chick embryo as medium, and antibodies appear in approximately one week. Protection lasts for many years. There is no specific treatment against this virus.

5. *Rickettsial Diseases*.—Endemic typhus compared to the epidemic typhus is a relatively mild disease. The American Public Health Association, however, advises vaccination of groups exposed, by occupation or residence, to unusual risk of contracting this disease.²⁴

The severity of Rocky Mountain spotted fever varies at different times and localities, due to the changeable virulence of the organisms. The vaccine, however, will at least modify the disease, although it may not always prevent it.

Vaccination against Q fever is not routinely used and is generally indicated only in persons occupationally exposed.

The active immunity conferred by these vaccines is usually of short duration, less than one year, and, if indications exist, yearly boosters should be administered. Antibiotics are highly effective against the rickettsial organisms, especially when given early in the disease. It is, therefore, not advisable to take the risk of using rickettsial vaccines in highly egg-sensitive patients.

CONCLUSION

The information obtained from drug manufacturers and health authorities has been summarized in table form. Despite the high incidence of allergy to horse serum, no substitute sera are available except for tetanus. Antitoxins and antivenins are the only effective therapeutic agents against diseases which, untreated, carry a very high mortality. Antibiotic agents alone are not sufficient. Although rabbit proteins rarely cause allergic reactions, satisfactory substitute sera are available. Chick embryo vaccines are used against diseases which are either rare or which respond well to antibiotics.

We feel that all efforts should be made to produce antitoxins and antivenins from sources causing fewer allergic reactions, and that toxoids should be used more extensively.

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THE PHYSICIAN'S READING

"We may then broadly classify the physician's reading as reading for *pleasure*, reading for *work*, and reading *out of duty*. With the first he learns to develop as a man and fly on the wings of the spirit; with the second he learns to master his profession, navigating with the sails of his knowledge; and with the third he learns how to become worthy of his country and of his period, thus leaving behind him a cultural mark on the face of humanity."—F. MARTI-IBANEZ, *Books in the Physician's Life*, MD Publications, Inc., October, 1955.

PERFUME DERMATITIS

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IN THE CASE of skin reactions by perfume materials, one is concerned, as a rule, with phenomena in the category of allergic hypersensitivity rather than in that of primary irritation.

Allergic sensitivity to perfume, like any other form of cosmetic allergy, depends upon a variety of factors. Thus, certain types of skin are more likely to respond with manifestations of sensitivity than others.

While protein participation is usually involved in antigenic action, various substances, other than proteins, can act as antigens. In fact, some simple organic chemicals can produce sensitization phenomena, following intracutaneous injection or topical application to healthy skin.¹⁻⁵ The capacity of a simple substance to act as an antigen is assumed to depend upon its combining ability, whereby an originally "native" protein becomes "foreign" and therefore antigenic.

SENSITIZATION STUDIES

This is relevant to a brief but highly significant report by Landsteiner and Jacobs in the matter of a perfume material, viz., methyl heptine carbonate. Some time ago, H. L. Baer⁶ connected a case of lipstick dermatitis with the occurrence in the lipstick perfume of methyl heptine carbonate. Similar findings were made by Hoffman and Peters,⁷ as well as by others. Alerted by these reports, Landsteiner and Jacobs⁸ carried out a series of sensitization experiments which proved that guinea pigs could indeed be rendered specifically sensitive to this chemical, following several exposures at weekly intervals to its dilute solution in olive oil, either in the form of an intracutaneous injection or in that of an inunction of the unbroken skin. The specificity of the imparted sensitivity was evidenced by the failure of other chemicals possessed of marked sensitizing capacity (e.g., 2, 4-dinitrochlorobenzene, 2-4-dinitrobenzylchloride, o-chlorobenzylchloride) to produce any significant reaction upon the skin of the sensitized animals.

Although no attempt was made to demonstrate any reaction *in vitro* between methyl heptine carbonate and a protein, Landsteiner and Jacobs assumed that the former chemical was made to react *in vivo* with some protein so as to effect the latter's conversion into a specific antigen.

While the above is an example of singular specificity in sensitization, there exists also a group specificity which is evidenced in the case of chemically related substances capable of giving rise to antigen formation.

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PERFUME DERMATITIS—KLARMANN

In other words, if sensitization is achieved by a particular substance, a dermal reaction may be elicited by another substance structurally related to the sensitizer.

The latter is relevant to another series of highly indicative experiments carried out by Keil.⁹ His interest has been attracted to this problem by some cases of dermatitis attributed to citronella oil which already had a record of inciting dermatitis in susceptible individuals.¹⁰ The patient who was found originally to be sensitive to citronella oil was now patch-tested with oil of lemon; again he responded with a positive reaction. In an endeavor to ascertain the offending principle, Keil applied one per cent solutions of several constituents of citronella oil; he obtained strongly positive reactions with citronellal, and weaker positives with citronellol, citral, geraniol and geranyl acetate. The same results were obtained in two other cases.

In order to make sure that the patch test results were due to specific sensitization, Keil applied lemon oil as well as the several single compounds listed to twenty-six control subjects afflicted with different skin ailments totally unrelated to the citronella oil type of dermatitis. Negative responses were obtained in twenty-three cases, and mild positive responses in three cases. This finding tends to support the postulate of specificity of the substances tested.

One of Keil's patients, who was sensitive to oil of lemon, was found to give a positive reaction also with oil of turpentine. Because of this, tests were run on this individual with solutions of *alpha*- and *beta*-pinene. Positive reactions were obtained with both isomers, *beta*-pinene being by far the stronger agent. The latter is a close chemical relative of limonene; this furnishes the explanation for the sensitivity to both lemon oil and turpentine.

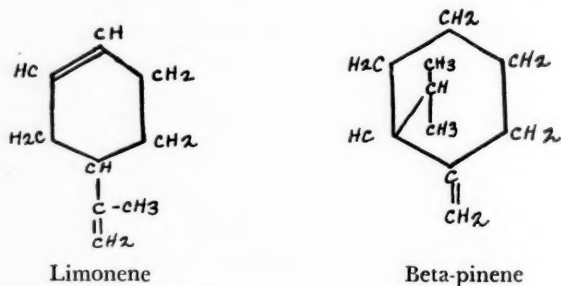


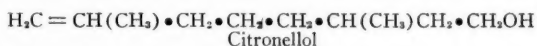
Fig. 1. Structural formulas of limonene and *beta*-pinene.

In comparing the structural formulas of limonene and *beta*-pinene, one observes that both have an exposed methylene radical; their reactivity resulting in eventual sensitizing action might well start at this point.

It was mentioned previously that the aldehyde citronellal appeared to

PERFUME DERMATITIS—KLARMANN

act as the primary allergen of oil of citronella. The synthetic hydroxycitronellal also produces a positive reaction although somewhat weaker. The unsaturated alcohol citronellol is a strong reactant possibly because of its similarity to citronellal with regard to the end position of a methylene group which is found also in the case of limonene and *beta*-pinene. By contrast, geraniol gave only a weak reaction in spite of its unsaturated character, and this was true also of citral which is in the same relation to geraniol as citronellal is to citronellol; the reason is possibly to be sought in the substantial absence of a reactive methylene end group in geraniol as well as in citral.



In addition to the relationships between chemical structure and sensitizing action of some individual compounds, Keil's work suggests the existence of group reactivity, in that persons sensitive to oil of citronella may be equally unable to tolerate exposure to the essential oils extracted from the other members of this botanical family, such as the oils of lemon-grass, palmarosa, and gingergrass. However, the cross sensitivity may extend to oils of unrelated botanical origin whose chemical composition bespeaks their reactivity, such as oil of *Eucalyptus citriodora* (consisting almost entirely of citronellal).

A reported case of dermatitis caused by oil of geranium¹¹ probably belongs in this chapter, also a case of cheilitis due to the presence of geranium oil in a lipstick perfume.¹² Some evidence points to the reduced sensitizing action of terpeneless oils.¹³

DIGEST OF PERFUME SENSITIVITY DATA

Unfortunately, only a very few papers have been published permitting a systematic insight into the subject of our discussion. Most of the other papers are essentially case reports identifying perfume or perfume ingredients as sensitizing agents, or else some "wholesale" reports of tests performed in a manner virtually precluding either theoretical or practical utilization of the information obtained.

Following are some reports belonging in the former category:

One of the earliest papers by Freund¹⁴ deals with the so-called Berlocque dermatitis, a condition attributed to the use of the classic type of Eau de Cologne. The inciting agent appears to be bergamot oil. However, Berlocque dermatitis and the concomitant skin pigmentation are not the sequelae of a simple sensitization, but rather the results of a combination of factors in which irradiation by sunlight plays an essential role. This condition has been observed and reported upon by several investigators, both in this country and abroad.¹⁵⁻²¹ Rogin and Sheard suggested that

chlorophyll or some adulterant may be responsible,²² but this is not in agreement with the findings of Giraudeau and Acquaviva²³ who definitely exclude chlorophyll and linalyl acetate as causative agents, although they did demonstrate that oil of bergamot sensitizes to visible light within the range of 3900 to 6000 Angstrom units, i.e., from the violet to the yellow part of the solar spectrum. According to Goodman²⁴ the presence of traces of copper in the oil, originating from the shipping containers made of copper, is necessary for the sensitization reaction to take place.

Recent experiments by Lerner, Denton and Fitzpatrick²⁵ indicate that it is the psoralens present in a variety of natural essential oils (including bergamot oil and other citrus oils) which are responsible for the hyperpigmentation of Berlocque dermatitis.

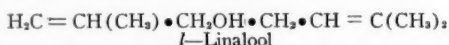
An interesting observation by Urbach and Kral deserves mention at this point, viz., that internal ingestion of vitamin C prevents photosensitization by oil of bergamot.²⁷

It is known now that oil of bergamot does not stand alone as a factor in photodermatitis. Other essential oils, both of the citrus type as well as those belonging to other categories, have been recognized as photosensitizers. Among them is oil of lime which causes pigmentation upon exposure to sunlight. As shown by Sams,²⁵ the pigmentogenic action appears to reside in the longer wavelengths of the ultraviolet radiation, just below the zone of visible light (3100 to 3700 Angstrom units). While the nature of the photocatalytic agent remains undetermined, doubt is raised as to the participation of copper as suggested by Goodman in the case of bergamot oil, since the reaction is produced with freshly expressed or extracted oil.

Oil of neroli is a photosensitizer, as is oil of petitgrain.²⁸ Although of lesser significance in perfumery, oil of cedarwood acts in a similar manner, producing a photosensitization type of dermatitis,²⁹ sometimes associated with pigmentation.³⁰

Oil of lavender has been identified by Finkenrath³¹ as the cause of simple sensitization dermatitis (without exposure to light being necessary), and pigmentation of the skin following topical application has been reported by Szanto.²⁸

Other essential oils suspected or accused of sensitizing capacity are the oils of rosemary, angelica, cassia, calamus, eucalyptus, orange, anise, bay, bitter almond, cade, ylang-ylang, carrot seed and linaloe;³² with respect to the last-named oil, the capacity for sensitization may reside with *l*-linalool which, like the sensitizing citronellol, has the methylene group in an end position:



Of course, mention of photodermatitis is made here only with direct reference to the participation of the several essential oils in this picture. However, this is not deemed to be the place for dealing with the much

broader aspects of photodermatitis, or even with the more limited aspects of phytophotodermatitis.

If one concedes that essential oils may act as irritants, then Peck's³³ observations are relevant to the phenomenon of pigmentation, since it has been shown that the latter can be produced without the contributory factor of sunlight.

As to oil of orris, it seems that most objections to its use stem from the well-recognized allergenic character of orris root which, in dried and powdered form, had been used, some time ago, as an ingredient of face powders and other cosmetics. However, no cases of allergy appear to have been reported as being directly associated either with oil of orris or with orris concrete.

The selective action of an essential oil in creating a limited area of dermal response to its sensitizing effect has been reported by Cummer.³⁴ His patient was in a habit of dropping some cinnamon-flavored liquid dentifrice in the palm of his left hand, and picking it up with a toothbrush; the excess was allowed to run off between the fingers to the dorsum of the hand. An erythematous-vesicular eruption occurred in the interdigital spaces of the hand, but at no time was there any evidence of irritation of the mouth, lips or face. Patch testing with the ingredients of the dentifrice confirmed the causal involvement of oil of cinnamon and, incidentally, elicited a mild positive reaction to oil of spearmint.

Some perfume materials have the bad reputation of being irritants or sensitizers, although the pertinent information appears to be more putative than experimental or clinical in character. This comment applies, e.g., to eugenol and isoeugenol, concerning which little directly applicable information is available.³⁵⁻³⁷ Incidentally, isoeugenol (4-propenyl guaiacol) is thought by some to be less of an offender than eugenol,³⁸ while others would like to see its use avoided.³⁹ Since both eugenol and isoeugenol are phenol derivatives of comparatively low molecular weight, it is conceivable that in concentrated form they might have a direct or primary untoward effect upon the skin; the same would be true of the carnation or spice type of perfume compositions in which either or both might occur. It is questionable, however, whether this has any direct relevance to their employment in scents for creams, soaps, et cetera. Reference has been made above to the molecular weight of phenol derivatives, because it is known that the toxicologic action in the series of phenol homologs decreases as their molecular weight increases.⁴⁰

Heliotropin has been implicated as a possible cause of dermatitis⁴¹ and its use in lipstick perfumes is being discouraged.⁴² Skin irritant action has been attributed to methyl anthranilate.⁴²

A somewhat special position is occupied by oil of wintergreen, consisting substantially of methyl salicylate, because of its ready penetration through the skin. According to Macht⁴³ and Harry,⁴⁴ however, this oil is not

PERFUME DERMATITIS—KLARMANN

unique in its penetrating capacity; other essential oils, too, are effective penetrants with a potential for physiologic or pathologic effects.

There are also some case reports of reactions to finished perfumes. Thus, Tobias⁴⁵ mentions one such case in which a well-known perfume caused dermatitis after prolonged usage. In connection with this case, he stressed the applicability of the antigen-antibody principle in view of the occurrence of an incubation period of six months which finally ended with a cutaneous display of acquired hypersensitivity. A case of dermatitis attributed to a jasmine bouquet type of perfume was reported by Bloom.⁴⁶ In this case, the offending agent was found to be benzylidene acetone. Von Varga⁴⁷ presented a case of hypersensitivity to a hyacinth perfume. A report by Feiler is interesting as well as amusing because, in this case, the offending perfume was one distributed by a house specializing in "hypoallergenic" cosmetics.⁴⁸

The type of paper referred to before which offers but little by way of utilizable information is that by Patterson and Hall,⁴⁹ subsequently expanded by Katz.⁵⁰ These papers merely list a whole series of essential oils and aromatic chemicals which were applied either in pure form or (in the case of crystalline substances) in the form of saturated alcoholic solutions, under a closed patch, to the inner portion of the lower arm. The results indicate at best that most of the essential oils and aromatic chemicals tested should not be regarded as primary irritants, although some of them did produce a skin reaction in isolated instances. In some cases, as, e.g., in that of methylnonylacetaldehyde, a cutaneous reaction may appear in one to five days following application. It is regrettable that this type of study has not been enlarged in scope; certainly a single application of a number of undiluted perfume materials to the human skin bears hardly any relevance to the problem with which one is concerned here.

ALLERGENIC EFFECTS OF INHALED PERFUMES

A special position is occupied by the allergic phenomena elicited without direct exposure of the skin to the sensitizing action of perfume or of perfume ingredients. It is well known that inhaling the perfume of certain flowers, such as roses or lilac, may cause sneezing or rhinorrhea in sensitive individuals, and there is adequate evidence in support of the contention that this is due to some volatile components of the floral oil rather than to pollen.⁵¹ Urbach⁵² demonstrated the existence, in some cases, of a purely nasal hypersensitiveness to the essential oils of lemon, orange and tangerine, also to oil of pine needles without any concomitant cutaneous response; in other cases, nasal and cutaneous reactions were found to run parallel.

Evidently, infinitesimal traces of some odoriferous materials possess the allergenic capacity of eliciting both respiratory and dermal responses. Very little pertinent information has come to light from the field of perfumes although, judging by the observations reported with other odorous

materials, this type of hypersensitivity should be encountered more commonly. As to some of the related phenomena, reference may be made here for illustrative purposes to the reported cases of a hypersensitiveness to the inhaled aroma of coffee⁵² and of certain vegetables⁵³ producing respiratory or cutaneous symptoms.

It is of possible interest that, in one case of hypersensitivity to the perfume of locust blossoms, desensitization of the patient could be effected by feeding of a seventy-two hour enflourage of these blossoms in lard over a period of two weeks. This procedure prevented the severe "hay fever" symptoms from which the patient had been suffering previously, in spite of almost continuous exposure as occasioned by living in a locust grove.

DISCUSSION

The several instances presented here may furnish an idea as to the probable size of the field yet to be explored. By way of giving just a few examples of what needs to be learned, one might point to the very small number of perfume materials studied to date for their irritant or sensitizing potentials, and of the concentrations in which these potentials become manifest in the form of clinical dermatitis. In this connection, hardly anything is known concerning the existence of sensitizing synergisms or antagonisms of groups of perfume materials (floral and essential oils, aromatic synthetics, et cetera) which are, of course, the fundamental entities of all perfume formulas. Next one might stress what must be a marked difference between the transitory or fugitive effect of the application of a perfume or toilet water on one hand, and the fixation of a perfume to the skin by means of some vehicle such as a cream, a lipstick, a face powder, et cetera, on the other. Furthermore, hardly anything is known concerning the influence of the various cream and emulsion types upon the dermal effect of the many perfume ingredients with which they may be scented; in this connection, there come to mind studies on skin absorption such as those carried out by Harry⁴⁴ which might well lend themselves for adaptation to the problem under discussion, especially in view of his finding that certain essential oils show the greatest capacity of skin penetration, greater than that shown by the most active vegetable and animal oils or fats studied. And what about the possibility of a contributory effect of perfume in the case of cosmetics with admitted dermal action, such as antiperspirants? Since soaps and detergents are now known to affect skin morphology and physiology, what added effect is produced by the perfume in these vehicles, and how should one select a perfume for them? The number of open problems is really legion.

In his endeavor to eliminate allergenic or sensitizing ingredients from his formulas, the cosmetic chemist has been, on the whole, quite successful. However, the perfume presents a problem both *per se* and as a component of cosmetic formulas; there is a general feeling that, where cosmetic sensitivity is encountered, perfume is quite likely to be involved.

PERFUME DERMATITIS—KLARMANN

The evidence in this matter may appear to be more indicative than supportive at the present time. The reason for this is to be sought in the dearth of published relevant information probably due to the comparative mildness and transitoriness of the dermal symptoms offering but a moderately interesting stimulus to the dermatologist who is more likely to be attracted by true skin pathology as an object of study. The complexity of the perfume formula is also apt to act as a deterrent. Nevertheless, a first corrective step appears to have been taken recently in the direction of creating perfumes with a low sensitizing index, through the selective use of components (essential oils, chemicals, resins, et cetera) which have been specially purified, and screened by patch tests for their fitness to serve in such perfume formulas.⁵⁴

Some pertinent comment may be in order here on the subject of "hypoallergenic cosmetics." To the extent that in its strict meaning this term implies freedom from acknowledged or suspected allergenic agents, it could probably be applied to any cosmetic preparation formulated by an informed chemist and produced under proper sanitary manufacturing conditions. Yet cosmetics marketed specifically under the "hypoallergenic" designation are usually made available perfumed as well as unperfumed, with an increasing trend toward the latter type as fostered by some dermatologists and allergists who have become aware of the perfume's capacity for sensitization, and who now wish to exclude this apparently significant source of allergic reaction, when indicated by the patient's relevant condition.

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Submitted June 5, 1957

USE OF PENICILLIN FOR MASTITIS

"The Federal Food and Drugs Administration is enforcing new regulations regarding penicillin in mastitis ointments.

"The new regulations require that no single dose of mastitis ointment can carry more than 100,000 units of penicillin. Formerly, some ointments contained as much as one and one-half million units per dose.

"The reason for the regulation is that a recent Federal Food and Drug survey indicated that too high a percentage of market milk contains penicillin. Unless this percentage is reduced, the antibiotic agent will be banned in mastitis ointments.

"The regulations also state that every ointment tube label must warn dairymen to withhold from market for at least three days all milk from treated cows. It takes at least 72 hours for the penicillin to work its way completely out of the udder."—*The Farmer's Digest*, January, 1958.

CHROMATE SENSITIVITY

Differentiation of Specific and Nonspecific Positive Patch Tests*

L. EDWARD GAUL, M.D.
Evansville, Indiana

DIFFERENTIATION between specific and nonspecific positive patch tests in cases of chromate sensitivity was determined in a survey of 844 patients over a three-year period. The patients were patch tested with a series of metal salts, and 100 were simultaneously tested with the corresponding metal disks. There were 667 negative reactions to tests with potassium chromate solution 1 per cent. This strength stained the skin yellow, yet no evidence of primary irritancy was seen. The concentration recommended in the past for patch testing has varied from 5 to 0.1 per cent; but, although 0.5 per cent is now believed adequate, I have continued to use one per cent in order to establish its range of reactivity. This was considered a vantage point from which to observe specificity. There were seventy-seven positive tests. The responses were erythematous in twenty-eight, urticarial in twenty-eight and eczematous in twenty-one. The goal was to do as much test screening as possible in each patient. Often this ambition was not realized. Some patients allowed complete study; others consented to only a few tests. Too often, the initial series provided a basis for further tests, but the patient declined. Almost all the metallic salts were used. Special attention was given to follow-up observations in all positive tests.

ERYTHEMATOUS REACTIONS TO CHROMATE

Of the twenty-eight patients, thirteen were men and fifteen women. The hands of nineteen patients and the hands and feet of three patients were involved. Three patients presented chronic flexural dermatitis. Usually, the erythematous reaction flared two to three centimeters. The color was similar to a nevus flammeus. The reaction appeared deep-seated. There was no itching. The reaction subsided in about three days and left no trace. Inspection of the site at later dates would sometimes disclose a few pinpoint sites of excoriation.

Reports of typical cases

Case 1. Mercurial sensitivity inducing nonspecific chromate response—S. K., a white school girl, aged sixteen, was seen for an acute erythrodermia affecting the face and neck. She was hospitalized and a routine clinical review completed. The history was commonplace. An irritation on the nose from a cold was treated with ammoniated mercury 5 per cent to prevent infection. The ointment was two years old and belonged to her sister. About eighteen hours after application, a burning

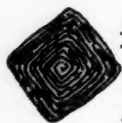
Dr. Gaul is an Associate Fellow of The American College of Allergists.

*Specific is used in the sense of being etiologic or diagnostic of the presenting dermatitis.

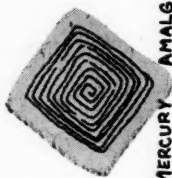
PATCH TESTS

ELASTOPLAST STRIP

CONTACT TESTS

 HgCl_2 1%

Amm. Hg. 0.1%

 K_2CrO_4 1%

MERCURY AMALGAM

 Na_2SO_4 1% HgCl_2 0.01% HgCl_2 1% PbCl_2 1% HgCl_2 0.1%

THRESHOLD TEST .0001%

Fig. 1. The tests were placed on the left thigh about 5 P.M. They were removed the following morning because of itching. At the site of chromate, there was a bright erythema with sufficient edema to cause the reaction to have a convex appearance similar to a watch glass. At the same time, there was noted on the left wrist, where a wrist watch with a metal expansion band had been worn, a band of erythema outlining the strap. This had been removed by the patient during the night because of burning. The same evening, or about nine hours later, the test area was inspected, and the chromate reaction had now disappeared leaving no trace of its presence, so had the erythema outlining the watch band. The specific sensitizer in this patient was mercury. Notice the threshold test concentration. Mercury amalgam produced as much embossed vesiculation as ammoniated mercury, 0.1 per cent. She was sufficiently sensitive to develop a flare of erythema to a contact test with mercuric chloride 1 per cent and a slight papular erythema to a dilution of 0.1 per cent.

CHROMATE SENSITIVITY—GAUL

redness developed around the nose, which rapidly grew worse. A mercurial sensitivity seemingly had existed for fifteen years because ammoniated mercury had produced a severe dermatitis in infancy, and there had been another attack on the right leg at the age of six, after treatment of a cut with an organomercurial. On the second hospital day, patch tests were done and the results are sketched in Figure 1.

Comments.—When this patient had been well for approximately one month, patch tests were done on the opposite thigh with potassium chromate 2 per cent and 0.1 per cent. These tests were nonreactive. Contact tests were done with potassium chromate 5 per cent and 1 per cent. These, too, were nonreactive. If there had been no awareness of mercury sensitivity, and tests had not been performed with a mercurial, how easy it would have been to consider a sensitivity to chromate and, what is more, the dermatitis on the wrist would have been thought due to the metal wrist band. It is believed that the exquisite sensitivity to mercury—threshold of 0.0001 per cent—induced a cutaneous hyperreactivity of sufficient degree to allow other allergenic chemicals readily to provoke nonspecific reactions.

Case 2. Benzocaine sensitivity inducing a nonspecific chromate response—G. B., is a white widow, aged fifty. Eight months ago, a rash developed on her left hand. It was diagnosed and treated as poison ivy. There gradually developed a diffuse psoriasiform dermatitis affecting the face, neck, upper torso and extremities. She was hospitalized for investigation. The chief finding was a mild diabetes. Patch tests were done on the abdomen, the only area of apparently normal skin. They are sketched in Figure 2.

Comments.—When this patient had been well for three months, a patch test was done with potassium chromate 1 per cent and a contact test with 5 per cent. These tests evoked no response and no delayed irritation. Apparently, organic compounds, like inorganic ones, can induce a similar hyperreactive cutaneous state. While this exists, nonspecific reactions can readily occur.

Summary.—Contact tests were performed in five patients with dilutions of 1 and 5 per cent of potassium chromate. These tests were nonreactive. Patch tests were performed in the same patients with dilutions from 0.001 to 0.2 per cent of potassium chromate. These tests, too, produced negative results. From this evidence, the erythematous response to chromate differs sharply from the eczematous one.

Coincidental Sensitivities

Inorganic.—Three patients showed concurrent reactions to nickel chloride 1 per cent, one to gold chloride 1 per cent, one to silver nitrate 1 per cent, one to copper sulfate 1 per cent, two to cobalt sulfate 1 per cent and four to mercuric chloride 0.1 per cent. Six patients showed reactions to one or more metal salts, which explains the numerical discrepancy. One patient was positive to a brass disk for a total of seven reactors.

Organic.—Three patients were sensitive to "caine" compounds, two to rubber products, two to perfume, one to dibeta-naphthyl-paraphenylenediamine, one to tetramethylthiuram monosulfide for a total of nine reactions. Thus, a total of eighteen out of twenty-eight patients (65 per cent) showed concurrent reactions to other metallic salts and a variety of organic chemicals. These reactions proved to be the etiologic contactant for the dermatitis. An erythematous patch test response to potassium chromate 1 per cent is thought to be a nonspecific reaction. It is an invitation to search painstakingly for the specific sensitizer that induced the cutaneous hyperreactivity.

CHROMATE SENSITIVITY—GAUL

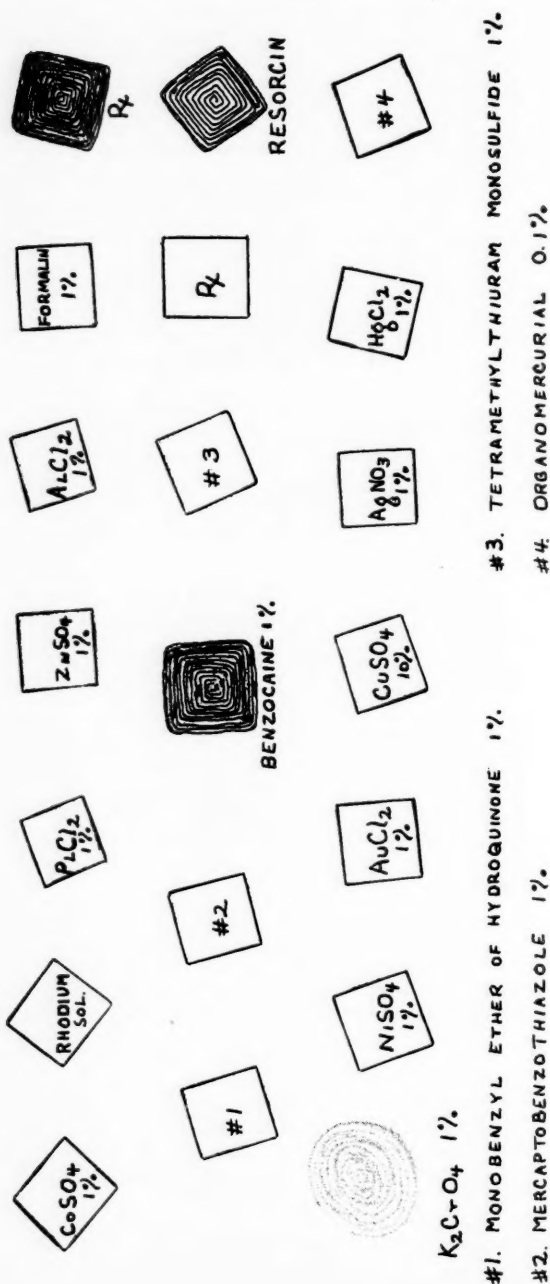


Fig. 2. The tests were read in twenty-four hours, and an embossed vesiculation had developed to benzocaine 1 per cent, also to the prescription—the composition of which was unknown—and to resorcin. The potassium chromate reaction was seen as a flare of deep-seated erythema, bright red in color. It disappeared completely in three days whereas the "caine" reaction persisted well over three weeks.

CHROMATE SENSITIVITY—GAUL

URTICARIAL REACTIONS TO CHROMATE

In this group were nine men and nineteen women. Seventeen patients presented extensive areas of dermatitis on the hands and forearms, axillae, face, neck and upper torso. Therapeutic sensitization was ever present.

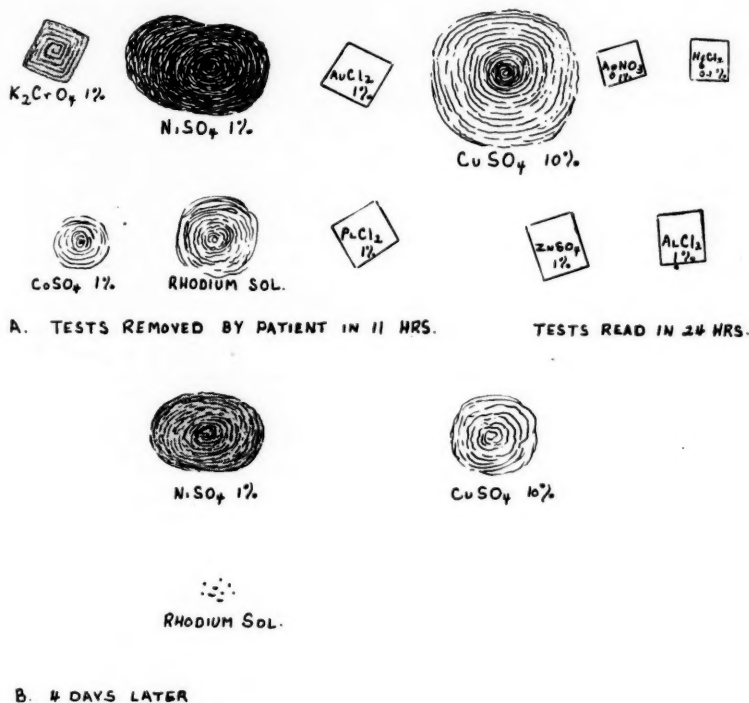


Fig. 3. This sketch illustrates the importance of a follow-up review of all patch test reactions. The nickel sulfate was considered the prime sensitizer because of the massed vesiculation and because of its persistence. The urticarial response to the chromate had disappeared sometime within four days. The copper sulfate had faded to a barely noticeable erythema. The cobalt sulfate had disappeared completely, and the rhodium solution had practically disappeared.

Seven patients' hands and feet were involved. Two patients suffered dermatitis of the neck and two of the anogenital region. Patch test developments approached the unusual. They were bright red with a flaring edema. Some reactions stood up like a dermatographism. The immediate and severe reactions promptly disappeared. It was disturbing to see these intense reactions, and several days later to find them gone with no trace of their initial violence.

CHROMATE SENSITIVITY—GAUL

Reports of Typical Cases

*Case 1. Nickel sensitivity inducing nonspecific urticarial response to chromate—*C. S., a white man, aged thirty-seven, had worked as a farmer, truck driver, and carpenter. Six months ago he obtained employment at a chrome plating plant. After working there two weeks, a dermatitis developed on the backs of the hands which was attributed to "acid." At the initial visit, he presented a papular, lichenified eruption having a flexural distribution quite reminiscent of atopic dermatitis. He said, "When I get hot, I itch and break out." He thought he had had poison ivy every summer as long as he could remember. Patch tests were performed and the results are sketched in Figure 3.

Comments.—The reaction to nickel persisted well over three weeks, and was classed as the specific sensitizer. In the presence of a hypersensitivity to one metal, there is a pronounced tendency for other metallic ions to be drawn into the reaction pattern. Nickel and mercury are prone to cause this. Either these metals render the skin supersensitive, or their chemical configuration is not distinct enough to produce a high degree of allergic specificity. It might also be true that sensitivity to metals is not as specific as it is to organic chemicals. An urticarial response to chromate is apt to indicate the presence of another and more severe metal sensitizer. Conclusions based upon tests with a series of metallic salts will provide more authentic information than those based upon tests with one or two. To suspect chromate or nickel sensitivity and test only with one of these risks non-specific findings. To assume that a presenting dermatitis is due to metal sensitivity on the basis of occupation can lead to astounding errors in diagnosis.

*Case 2.—Formalin sensitivity inducing nonspecific urticarial response to chromate—*T. G., is a white married woman, aged thirty-nine, who presented a papular, lichenified dermatitis affecting the hands, forearms, axillary spaces, neck and chest of about one year's duration. The initial patch testing with a series of metallic salts disclosed a flaring urticarial reaction to chromate 1 per cent, an embossed erythema to nickel 1 per cent and an erythematous flare to silver nitrate 1 per cent. It seemed that here was an instance of typical metal sensitivity. On the left thigh was a second patch, which comprised tests for rubber antioxidants and accelerators, also resorcin, a deodorant, oil of cade, formalin and benzocaine. When this patch was removed, there was present an edematous vesicular reaction to formalin 1 per cent. Forty-eight hours later, the metal reactions had about disappeared, but the formalin response had spread and was weeping. This response persisted over three weeks. These results pointed to formalin as the true sensitizer. The patient recalled no source of exposure in her home, but she was asked to search further. In the cupboard was a bottle of formaldehyde used in making flour paste for her Sunday School class.

Comments.—The specific sensitizer in this patient was formalin. Removal of exposure allowed a chronic dermatitis to undergo prompt involution. If the formalin had not been tested, the likelihood of other interpretations is plain to see. Searching for specific reactors is a worthwhile undertaking in recurrent or chronic dermatoses, or both. When the patient was well, contact tests with potassium chromate 1 per cent, nickel sulfate 1 per cent and silver nitrate 1 per cent were not reactive. A contact test with formalin 1 per cent was positive, as well as a patch test with the flour paste containing one teaspoon of formalin per quart.

Summary.—Nine patients were retested months to several years after the involution of the initial dermatitis. Contact tests with 1 and 5 per cent potassium chromate resulted in no response, nor did patch tests with dilutions of 0.001 and

CHROMATE SENSITIVITY—GAUL

0.2 per cent. This evidence further separates the urticarial from the eczematous group. The failure of reactions to appear suggests the possible loss of chromate sensitivity, but it is more likely that there was not a specific sensitivity in the first place. It is in this urticarial group that the possibility exists for nonspecific responses to cement, leather and probably many other metallic and organic compounds.

Coincidental Sensitivities

Inorganic.—Two patients reacted to nickel chloride 1 per cent, two to silver nitrate 1 per cent, one to copper sulfate 1 per cent, one to copper sulfate 10 per cent, two to cobalt sulfate 1 per cent, one to rhodium solution and seven to mercuric chloride 0.1 per cent, for a total of eight reactors. The discrepancy in figures is due to the fact that a number of cases reacted to more than one salt.

Organic.—Four patients reacted to "caine" compounds, four to topical antihistamines, two to formalin, four to various resins, one to perfume, one to chloroaceto-phenone (tear gas, not tested), one to solvent, one to germicidal soap, one to tannic acid, three to black and blue dyed materials for a total of twenty-two cases.

The large number of concurrent inorganic and organic sensitivities, twenty-four out of twenty-eight cases, 82 per cent, demonstrates that an urticarial response indicated a more marked cutaneous hyperreactivity than an erythematous reaction to chromate. It suggests another and, probably specific, sensitizer at work. This was found in twenty-four out of twenty-eight cases. Follow-up studies, recurrences, and opportunity for hospitalization favored the detection of the specific sensitizer, or the actual etiology of the dermatitis.

ECZEMATOUS REACTIONS TO CHROMATE

This group included three times as many men as women, sixteen to 5. All but one had dermatitis on the hands, and two patients had had attacks on the feet. The eczematous reaction in five patients consisted of a flare of erythema which was papular or became papular. The principal feature was persistence, ten days to several weeks. Itching was not noticeable. Doubt may be expressed concerning the specificity of these reactions. The eczematous reactions in sixteen patients were frankly vesicular. Some of these made one wish that the testing concentration had been weaker. The vesicles were deep-seated, tending to be conical shaped at the epithelial surface. Weeping developed in about half the cases. Itching was marked and some patients thought the rash had spread to their backs. Symptoms and signs in these reactions made them differ from others, but the tell-tale factor was duration of the healing time. Two to six weeks was average.

Coincidental Sensitivities

Inorganic.—Only one patient showed a positive test to mercuric chloride 0.1 per cent and an organomercurial.

Organic.—Two patients showed reactions to footgear fabrics. In the papular groups, one patient developed a positive reaction to silicone paper, and one to a dried sample of furniture polish. A tally of the reactors in this group was five, or 20 per cent.

Summary.—Patch test responses seen in chromate sensitivity varied significantly in signs, symptoms and duration. The eczematous response stood out sharply as

CHROMATE SENSITIVITY—GAUL

papules and/or vesicles, but more noteworthy was the duration. The reactions tended to reproduce the characteristics of the presenting dermatitis. Since most of the patients were men, a source of chromate exposure was easily found. Some patients noted that splashing of chromate solutions on their skin was followed by a "breaking out" at the site. This information suggested the performance of contact, open or drop tests.¹ A filter paper square moistened with potassium chromate solution 1 per cent was placed on the skin and allowed to dry. This test produced a vesicular response in all patients classified in the vesicular eczematous group. Dilution test reactions to the contact method were uncertain at 0.2 and negative at 0.1 per cent. Patch test reactions to dilutions of 0.1 were positive, but became uncertain at 0.01 per cent. This testing had been extended to include six more patients, a total of twelve, and gave similar findings. The evidence is fairly conclusive that a vesicular eczematous patch test reaction with potassium chromate 1 per cent will be associated with a vesicular contact reaction to 1 per cent, and such reactions indicate specific chromate sensitivity.

This evidence has an interesting bearing on chromate concentrations encountered in industry. Cleaning tanks can contain chromic acid in concentrations of 5 to 20 per cent; lithographing and plate departments, bichromate 1 to 2 per cent; press room, bichromate 0.5 to 1 per cent; radiator coolants, 0.3 to 1 per cent, and chromate plating, chromic acid 10 to 20 per cent. Not to be overlooked is the use of potassium chromate as an antirust agent in truck and automobile radiators. These concentrations are sufficient to cause recurrences and maintain chronicity in subjects specifically sensitive to chromate. The uncertainty or absence of contact reactions at dilutions of 0.1 or even 0.2 would seem to place chromate in a fairly low index as a sensitizer. This helps to explain why employees continue their working exposures in the presence of a chromate dermatitis on the hands.

Patients with the papular eczematous reactions were considered specifically sensitive due solely to the duration of their reactions. They failed to meet the rigid limitations of the vesicular group. One patient showed a positive patch test reaction to 0.5 per cent, but a negative response to a contact test 1 per cent. Two patients did not react to patch tests of 0.5 per cent or to contact test with 5 per cent. One patient did not react to contact with 5 per cent, but did show a papular erythema by patch test 0.1 per cent. One patient showed no contact reaction to 5 and 1 per cent, but did show a distinct erythema by patch test 0.1 per cent.

DISCUSSION

Sulzberger and Rostenberg² demonstrated that the skin of persons suffering from recent or active dermatitis due to previous allergy of the eczematous type was more susceptible to sensitization with new and nonrelated eczematogenous allergens. These patients are roughly twice as susceptible. Sulzberger³ commented that there are many polyvalent sensitizations; that is, sensitization to one substance is often accompanied by sensitization to others, either related or even unrelated. He cited the investigations of Bloch and the studies of Wedroff and Dolgoff, who showed that individuals possessing eczematous contact-type sensitivity were much more easily sensitized through experimental applications of new eczematogenous allergens than were normal individuals. Pillsbury, Shelley and Kligman⁴ stated that clinical experience demonstrates the readiness of certain individuals to acquire multiple sensitivities, a phenomenon recognized under the designation of "polyvalent sensitivities" and/or "broadening of the

CHROMATE SENSITIVITY—GAUL

allergic base," and experimental studies show the sensitizations are more readily established in those with existing dermatitis regardless of its origin.

A report on metal dermatitis by Epstein⁵ recently appeared. Eighteen cases of chromate sensitivity were studied. He, too, employed a 1 per cent concentration for patch tests. Intradermal tests were done in these patients (0.05 cc of a 1:100,000 dilution) with potassium dichromate. All but two of the patients reacted to the tests. It was interesting that the dilutions used for intradermal testing were considerably below the epidermal threshold of chromate sensitivity by patch test 0.1 per cent and contact test 1 per cent.¹ Pirila⁶ determined threshold hypersensitivity to chromate in thirty-five patients. It was 0.5 per cent in one case, 0.2 per cent in four cases, 0.1 per cent in twenty-five cases, 0.01 per cent in four cases, and 0.001 per cent in one case. Pirila⁷ is of the opinion that there has been confusion as to specific and nonspecific sensitivity in metal dermatitis. He especially feels that many reactions to cement which have been interpreted to be allergic are actually toxic in nature.

It is apparent that the etiology of contact dermatitis is much more complicated than securing positive patch tests. The allergen inducing the hypersensitive condition needs to be discovered. Evidence is that patch test reactions to chromate that displayed erythema (1+ plus), erythema and edema, or urticaria (2+ plus) were nonspecific. These reactions developed because the tests had been performed on hyperreactive skin. In a fairly high number of patients, specific sensitizers were found to account for the hyperreactive state. The real chore in contact dermatitis is not the detection of the little culprits, but to find the big one. When this is found, the reward is bountiful.

SUMMARY

A specifically positive test for chromate sensitivity has the following features:

Contact Test.—Potassium chromate 1 per cent produces a vesicular reaction within forty-eight hours which persists over a week.

Patch Test.—Potassium chromate solution 1 per cent produces a vesicular reaction within forty-eight hours, usually much less, and the signs persist two or more weeks. A solution of 0.1 per cent can be used, but this concentration borders the threshold level. An erythematous and urticarial patch test reaction to potassium chromate solution 1 per cent suggests a hyperreactive state in dermatologic patients. These responses warrant additional investigations for other specific sensitizers which may be either inorganic or organic in nature.

Concern about specificity is important for establishing the true incidence of chromate sensitivity. A negative patch test result is decisive, whereas a

CHROMATE SENSITIVITY—GAUL

positive test reaction requires investigation for specificity. Considerable evidence shows that in metal sensitivity the skin does not meet the exigencies of weather with the same facility as normal skin, and there is increased susceptibility to irritation from environmental, physical and chemical agents.

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Re-Submitted: September 13, 1957

ON BIBLIOGRAPHIES

"Nevertheless, the bibliography of a subject should be investigated with moderation and remain a means rather than an end. There are occasions when bibliographical research may be carried on more deeply, for example, when those investigations imply special difficulties, as in the case of oriental manuscripts, but these exceptions should not become the rule. Bibliographical extravagance is a sin rather than a virtue, a real perversity; it is the fruit of pedantry, or if not, it must inevitably lead to it. Whenever the knowledge of a subject is sacrificed to a knowledge of its bibliography we may be sure that there is something wrong with the author, and his bibliographical results deserve less confidence than if he had devoted more time to the study of the subject itself and less to the bibliography of it. Indeed, such immoderate scholars give up precious realities for shadows; they make one think of the fools who to the delusive hope of wealth sacrifice all that makes life worth living."—GEORGE SARTON, *The Study of the History of Mathematics*. New York, Dover Publications, Inc., 1957, copyright 1936.

SURVEY OF AIRBORNE POLLEN AND MOLD SPORES IN ISRAEL

1954-1955

ARTHUR KESSLER, M.D.

Tel-Aviv, Israel

A SURVEY of slide observations, counting pollen and mold spores in the center of Tel-Aviv-Jaffa through the years 1951-1953; was given in two previous reports published in the ANNALS OF ALLERGY, Vol. 11, No. 3, 1953, and Vol. 12, No. 3, 1954. This report covering 1954 and 1955 brings the five-year survey to an end. It adds some comparative figures from other parts of Israel and conclusions drawn from the study.

In 1954, the climatic conditions, influencing time and intensity of pollination and the quantity of mold spores in the air, were about average. Seasonal winter rains were equally distributed over the rainy months from November to April. Their quantity was slightly over average, (604 mm in sixty-two rainy days).

The pine-pollination curve (Fig. 1) rises in mid-February, reaches a peak at the end of that month, and thereafter reflects the incidence of rainy and sunny periods.

The pollination of grasses (Fig. 2) which started early in March was then delayed by rains later in March and early in April. As in 1953, grass pollination reached its peak at the end of April, continued heavily in the first days of May and then ended abruptly. In autumn there were, at least in the town, no pollens of grasses on the slides.

The similarity of the curves of mold spores (Fig. 3) throughout the survey is striking. The first rise, almost solely attributable to *Alternaria* spores, occurs in April, May and June. The second and lesser rise occurs in autumn. The quantities of *Alternaria*, *Macrosporium* and *Helminthosporium* are identical to those of the preceding year. Apart from the counted mold spores, *Hormodendrum* was the most frequently found, in chains or large branched formations. In the humid days of July and August *septate hyphae* grow out from *Alternaria* already on the slides. Isolated *septate hyphae* were frequently found.

The blooming season is earlier in the plains under sea level, around the Genesareth Lake, in the Jordan Valley and in the Valley of Beitsan, than in the hill regions. For three days, April 2, 3, and 4, when the blooming season on the coastal plain had just commenced, there were counted on slides in the region of the Genesareth Lake (Tabha, 110 m under sea-level), in an area over 18 x 18 mm fifty-six pollens of grasses, two pine pollens, plentiful pollens of citrus and cypress trees, and of the Compositae family. Molds were the same type as in the plains and were plentiful. During those three days, there accumulated on slides from the same area,

POLLEN AND MOLD SPORES—KESSLER

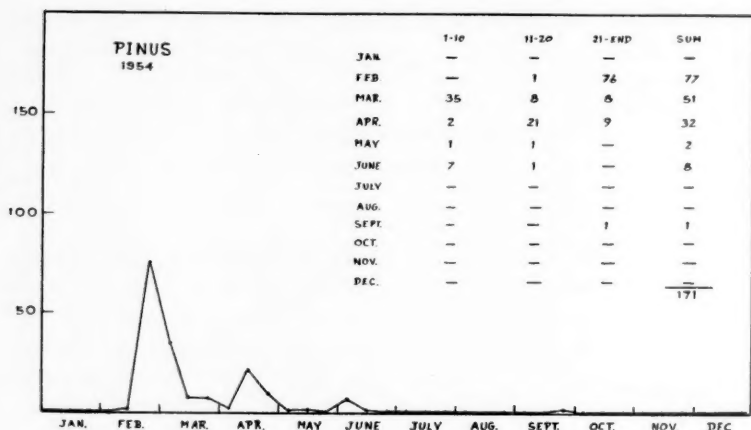


Fig. 1. Incidence of pine pollens in the center of Tel-Aviv-Jaffa, 1954.

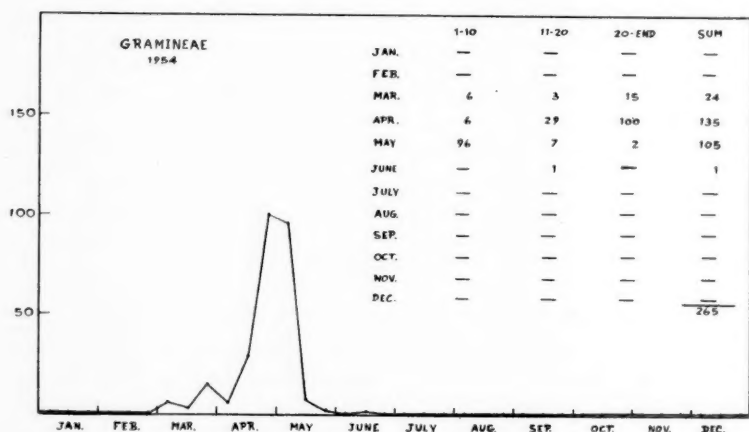


Fig. 2. Incidence of grass pollens in the center of Tel-Aviv-Jaffa, 1954.

sixty-eight *Alternaria*, 105 *Macrosporium*, two *Helminthosporium*, abundant rusts, smuts, and *Hormodendrum*.

Observations at the same time in the upper Galilee (Kfar Giladi), though done on rainy days, showed the same pollen and molds in lesser quantities.

On the hills of Jerusalem (Kiriath Anavim, 800 m above sea level) blooming time occurs later than on the coastal plain. Slides were exposed there daily during the spring blooming time from May 2 until May 7. For those six days the sum of grass pollens on the area of 18 x 18 mm

POLLEN AND MOLD SPORES—KESSLER

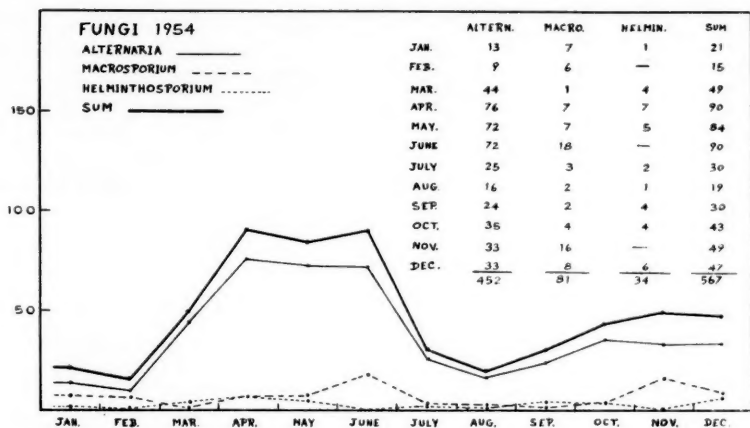


Fig. 3. Atmospheric incidence of macroconidia of fungi in Tel-Aviv-Jaffa, 1954.

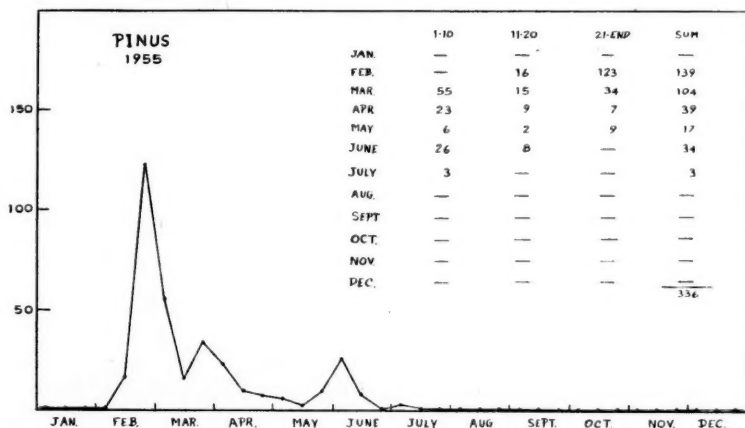


Fig. 4. Incidence of pine pollens in the center of Tel-Aviv-Jaffa, 1955.

was 106. In the same area, there were 134 pine pollens and some cypress pollens. Molds were the same as found in the coastal plain. There were seven *Alternaria* spores, two *Helminthosporium* and many smuts and rust.

Examination of an agricultural settlement on the coastal plain (Shfayim) showed, on September 28 and 29, in an area of 18 x 18 mm, six pollens of grasses. At that time Bermuda grass, the main source of grass pollens in autumn, blossomed in Shfayim. *Alternaria*, *Helminthosporium* and smuts were found on the slides. *Helminthosporium* were found in this region plentifully as plant parasites in stripe-like formations.

POLLEN AND MOLD SPORES—KESSLER

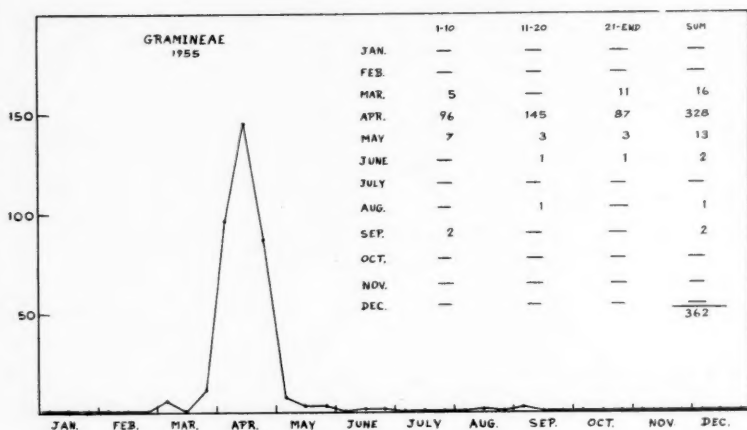


Fig. 5. Incidence of grass pollens in the center of Tel-Aviv-Jaffa, 1955.

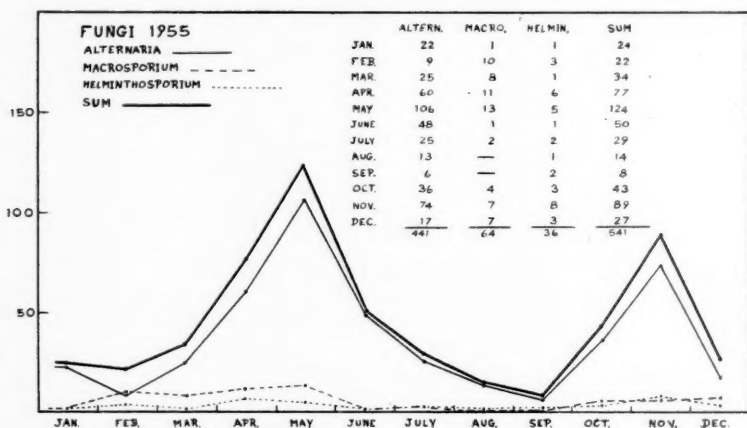


Fig. 6. Atmospheric incidence of macroconidia of fungi in Tel-Aviv-Jaffa, 1955.

The fifth year of the survey, 1955, was also average for the main climatic factors influencing the aerobiologic conditions. The rain months of November and December and a sunny January advanced the pollination of *Pinus* (Fig. 4) by some days. It reached a sharp peak in the last days of February. Rain, alternating with dry, hot weather (Hamsin) in March resulted in a widespread curve throughout March, April and up to mid-June. The total of this pollen was higher than in the previous year (336).

The pollination of grasses (Fig. 5) followed the usual pattern; starting at the end of March, with heavy pollination throughout April and decreasing in May. In August only a single grass pollen appeared on the slides.

POLLEN AND MOLD SPORES—KESSLER

The total of grass pollen for this year was 362. This approximates the average for previous years.

The two-hump form of the mold curve (Fig. 6) was especially clear in 1955. The first and higher rise was in April, May and June, the second, or autumnal, in October and November. *Alternaria* is, as seen before, the most prevalent mold on the slides. The totals of *Alternaria*, *Macrosporium*, *Helminthosporium* are astonishingly similar from year to year.

COMMENTS

This report concludes the five-year survey, employing slide observations and the standard gravity technique, of pollen and mold spores in Israel. Other aerobiologic findings were noted for comparison and further evaluation. The counting method was described in the first report (*ANNALS OF ALLERGY*, May-June, 1953).

The relation of the pollen counts to human pathology is known; for molds it was not attempted, because the connections are here much more complex.

Climatic conditions and the quantity and distribution of rain are noted. This is, for this region, the most important factor affecting the beginning and intensity of pollination. Another factor is the relative humidity. Days of low humidity (Hamsin days) had the highest pollination and a high mold count. The number of sunny days was not recorded because, except for the rainy season (November to April), almost all days are sunny. Wind velocity could not be tabulated although it is important to pollen and mold incidence surveys.

Pine-pollen counts are without significance in regard to pathology, but they are valuable because these pollens are easily recognized and counted, and the form of the pine-pollen curve indicates general pollination curves of other plants.

In 1951, a dry year, the curve is steep, high and the pollination short. The years 1952 and 1953 demonstrate low, widespread curves of rainy seasons whereas 1954 and 1955 had combinations of dry and rainy weather.

The most important aerobiologic event, for the workers in this field as well as for the many thousands of sufferers of pollen allergy, is the pollination of spring grasses. The influence of rainfalls is less direct in regard to this pollination, because its peak usually occurs later than the rainy season.

Therefore, the pattern in the five years is fundamentally the same, with some delay in 1953 and 1954 because of late rains at the beginning of April. In May, pollination is usually finished.

There are great contrasts in climate, topography and seasons for so small a country. Israel has mountains to the height of a thousand meters, near plains below sea level, and some of her most fertile areas border desert. These sharp differences change the time and intensity of pollination from

region to region. It is therefore possible, in spite of the size of the country, for inhabitants to avoid to some degree the peak of pollination.

Throughout the summer, Bermuda grass causes reactions in many patients whose occupation keeps them in irrigated places and in those who are especially sensitive. In autumn pollination of Bermuda grass causes a light second season, which is just noticeable on the slides, and its effect is more pronounced in the patient.

Mold curves for the five-year observation show some conformities. *Alternaria* is the most prevalent macroconidium. It gives the curve trough its monthly fluctuations the two-hump form, with a high peak in spring (April, May and June) and a lesser one in the fall (October and November). *Macrosporium* and *Helminthosporium* are to be found almost constantly and their fluctuations are less.

Hormodendrum is plentiful but it is not easily counted because its spores appear in branched chains and lumps on the slides. Single spores are practically impossible to differentiate by sight from other forms; but, on plates, every single spore grows to a culture, and a lump or a branchlike chain gives numerous cultures. With plate technique, *Hormodendrum* often shows the highest number of cultures in certain months, as indicated in the report for 1953. During the last four years the form of the curves and the total of the molds had a parallel relationship.

The fluctuations of smuts and rusts were already reported.

SUMMARY

The atmospheric incidence of the more important pollens and molds was examined in the center of Tel-Aviv (coastal plain of Israel) during five years (1951-1955).

The results were reported serially and demonstrated with graphs, statistics and comments.

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Submitted: September 12, 1957

DISCOVERY BY SYNTHESIS

It is an erroneous impression, fostered by sensational popular biography, that scientific discovery is often made by inspiration—a sort of *coup de foudre*—from on high. This is rarely the case. Even Archimedes' sudden inspiration in the bathtub; Newton's experience in the apple orchard; Descartes geometrical discoveries in his bed; Darwin's flash of lucidity on reading a passage in Malthus; and Einstein's brilliant solution of the Michelson puzzle in the patent office in Berne, were not messages out of the blue. They were the final co-ordination, by minds of genius, of innumerable accumulated facts and impressions which lesser men could grasp only in their uncorrelated isolation, but which—by them—were seen in entirety and integrated into general principles.—HANS ZINSSER, 1878-1940.

INHALANT ALLERGY IN INFANTS

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SINCE the pioneer days of medical investigation, it has been the custom to assume that practically all persistent respiratory conditions in infants are infectious in origin. The possibility of allergy has been considered only in the presence of such well-defined conditions as bronchial asthma and seasonal hay fever. Thus, today, it is the rule to treat these infants with one antibiotic after another; finally after weeks and months, when the last "wonder drug" has been used to no avail, the condition is labeled a virus with no specific cure.

Allergy should be suspected when a case history reveals that symptoms remain after many types of treatment, including antibiotic agents, vitamins, tonics to "build up resistance," frequent hospitalizations, a battery of laboratory tests, and numerous changes of physicians.¹ Urbach² was of the opinion that conditions classed as upper respiratory infection or sinusitis in children are often manifestations of allergy. Chobot³ regards vasomotor rhinitis the commonest allergic condition seen in children, often unrecognized as such, but interpreted as a common cold. Peshkin⁴ and Hughes⁵ also emphasize that respiratory allergy is common in children, but not regarded as such until the classic picture of asthma appears.

Allergic involvement of the respiratory system produces the following pathologic changes: edema of the mucous membrane, smooth muscle spasm, and excessive secretion of the mucous glands. The decreased activity of the ciliary action of respiratory epithelium and the excessive secretion of mucus result in the alteration of the normal protective mechanism of the respiratory system.^{6,7} The filtering, antibacterial, and cleansing⁸ action of the cilia and mucous blanket is lost, the barrier is let down, and infection ensues so that an ideal soil is prepared for the uninhibited growth of pathogenic bacteria. Edema and excessive mucus interfere with the normal drainage and aeration function of the Eustachian tubes, resulting in otitis media to complicate the entire picture.

The pediatrician and the generalist who cares for children are in an excellent position to recognize allergic respiratory conditions in their incipient stage, and by proper management to avoid eventual chronic disability in these patients. Feinberg⁹ states that modern pediatrics cannot be practiced without some knowledge and appreciation of the

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principles of allergy. Hansel,¹⁰ in a study of two hundred patients with nasal allergy and asthma, concluded that the majority presented allergic symptoms before the age of two years.

In infancy, the importance of food allergy has long been recognized, but hypersensitivity to inhalants is largely ignored. It is the opinion of the authors that inhalants, particularly house dust, are the most important cause of allergic involvement of the respiratory tract, even in the first two years of life. We are presenting a group of one hundred and fifty patients under the age of two years, treated with specific desensitization. All received house dust extract, some pollen extracts and respiratory vaccine. Every infant in this study had received the usual accepted measures to relieve their symptoms, but showed no improvement until desensitization was begun. These measures included antibiotics, antihistamines, cortisone at times, tonics, vitamins, x-ray therapy for enlarged thymus, elimination diets to rule out food allergy, and attempts at reducing the dust concentration in the home.

Hansel¹⁰ regards house dust as the principal offender in allergies of the respiratory tract. House dust is a conglomerate mixture representing allergic material from such agents as feathers, cotton, kapok, orris root, silk, animal danders, et cetera. Cohen et al¹¹ and Cazort¹² have shown that cotton linters represent an important part of house dust. The specificity of house dust has been recognized and repeatedly confirmed since Cooke's¹³ original report in 1922. It is only logical to assume that house dust is one of the earliest contacts encountered by the new born infant, since immediately after birth he is dressed with materials made of cotton or wool, and brought into an environment from which it cannot be eliminated.

The diagnosis of inhalant allergy was based on the following: (1) History of repeated respiratory involvement unimproved by the measures previously mentioned, (2) positive family history, (3) skin testing, (4) physical examination presenting signs of vasomotor rhinitis, (5) examination of nasal smears for eosinophils, (6) appropriate x-ray and laboratory studies, and (7) therapeutic use of house dust extract in an attempt to alleviate symptoms.

Skin tests were done by the rapid multiple puncture method, previously described by one of us.¹⁴ Positive reactions were confirmed by intradermal testing.

Treatment is instituted with the Endo house dust extract following the optimum dose method of Hansel.¹⁰ Initial dose ranges from 1:100,000,000 to 1:100,000. Very young infants and those with a definite history of wheezing are started on the weaker dose. We discovered early in this study that initial doses stronger than 1:100,000 consistently aggravated symptoms, regardless of weak local reactions. Intradermal injections are continued at four to seven day intervals, increasing the dose by .03 cc

INHALANT ALLERGY—WOOD AND WALKER

to a maximum of 0.3 cc. The patient is then started on a similar series of injections with a stronger dilution. The entire plan of therapy is based on the individual's response. Dosage is increased until symptoms are completely controlled, and this dose is maintained. With improvement, the interval between injections is gradually lengthened. In some

INHALANT ALLERGY IN INFANTS

Series of 150 Cases

Duration of Symptoms Prior to Treatment

Under 3 months	22%
3 months to 6 months	44%
Over 6 months	34%

Age at the Start of Treatment

Under 6 months	27%
6 months to 12 months	37%
12 months to 24 months	36%

Presenting Symptoms

Vasomotor Rhinitis	100%
Recurrent Otitis	38%
Wheezing	33%
Over 2 Hosp. Adm. for Resp. Inf.	25%
Eczema	14%
Gastrointestinal Symptoms	6%

Total Hospital Admissions for Respiratory Infections

Before Allergic Management	118
After Allergic Management	22

Skin Test Results

Positive to House Dust	62%
Positive to Pollens and Other Inhalants....	32%
Positive to Foods	56%

Results of Therapy

Excellent	62%
Good	30%
Unimproved	8%

infants, treatment is discontinued, but is resumed on recurrence of symptoms. The average duration of treatment in the age group described was one year.

In the investigation and management of these infants, we attempted to apply practical and time-saving methods, not as allergy specialists, but as practicing physicians realizing the importance of allergy in our respective fields. Seven infants in this study were referred to allergists in other localities, because we felt that they required a more complete investigation than we could provide.

During this study, the authors were impressed by the general lack of knowledge concerning the recognition of allergic problems. In eliciting the family history, when the question "Is there allergy in your family?" was asked, less than 20 per cent gave a positive reply. When asked

INHALANT ALLERGY—WOOD AND WALKER

about chronic sinus trouble, chronic bronchitis, nasal catarrh, et cetera, more than 90 per cent responded in the affirmative.

Not included in this study were twenty infants in whom investigation was begun, but who did not return. Some parents, and many of our medical colleagues as well, are unwilling to accept a diagnosis of allergy.

SUMMARY

The authors have presented one hundred and fifty cases of inhalant allergy in infants treated with specific desensitization. Results were excellent in 62 per cent, good in 30 per cent, poor in 8 per cent. All had previously received a variety of accepted therapeutic measures without improvement.

CONCLUSIONS

1. Allergy is a common cause of persistent respiratory involvement in infants. Inhalants, particularly house dust, are the principal offending agents.
2. Vasomotor rhinitis is the most frequent allergic manifestation in infancy, but too often is assumed to be an infection.

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SMOKING AND CHRONIC RESPIRATORY DISORDERS

Results of Abstinence

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CHRONIC cough is often attributed to smoking. Ordinarily nothing is done about it, probably because "smoker's cough" is assumed to be benign.

In this clinic, striking improvement in cough and ventilatory efficiency was noted in isolated cases after smoking was stopped. This was so impressive and there was so little in the literature about it, that a questionnaire was sent to forty-six patients whose records indicated improvement in chronic cough and other evidences of chronic lung disease after they stopped smoking. This brief report is based on an analysis of the records of the twenty-five patients who replied.

ANALYSIS OF CASES

The clinical diagnoses are given in Table I. The incidence and percentage of improvement of respiratory and other symptoms are summarized in Table II.

TABLE I. CLINICAL DIAGNOSES IN
TWENTY-FIVE SMOKERS

	No. of Cases ^a
Asthma	19
Allergic	3
Infectious	3
Mixed	13
Chronic pulmonary emphysema and fibrosis	13
Hay fever	10
Chronic pansinusitis	6
Bronchiectasis	2
"Chronic bronchitis"	2
	52

MISCELLANEOUS ADDITIONAL OBSERVATIONS

Four improved promptly, within one to five days. The average time for maximum improvement was five weeks. All of them gained weight, five to thirty-two pounds. The average age was forty-nine years, ranging from twenty-eight to seventy-one. They had smoked for from fifteen to forty-eight years, the average being twenty-eight years. The patients were observed for two to twelve years, the average being five years, after

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SMOKING—SWINEFORD AND OCHOTA

TABLE II. INCIDENCE, DURATION AND IMPROVEMENT OF SYMPTOMS IN TWENTY-FIVE PERSONS WHO STOPPED SMOKING

Symptoms	Incidence	Mean Duration in Years	Improvement						
			Excellent		Good	Fair	Poor	Improved	None
			100	90	75	50	25	Percent Not Known	
(a) Respiratory									
Cough	25	14	7	9	2	1	2	4	0
Dyspnea on exertion	24	11	1	4	3	5	5	4	2
Asthma	19	16	3	4	5	1	2	1	3
Frequent colds	18	12	2	4	3	2	2	3	2
Chest pain	11	11	3	2	1	1	1	1	2
Hay fever	10	11	2	3	1	0	0	0	4
	107		18	26	15	10	12	13	13
(b) Other									
Nervousness	20	9	1	2	2	4	4	4	3
Lack of energy	19	7	1	3	3	2	3	3	4
Sleeplessness	13	11	2	3	3	1	1	0	3
Poor appetite	12	5	2	5	0	3	0	2	0
Palpitation	9	7	2	2	0	0	2	1	2
Leg cramps	7	5	2	0	0	0	3	0	2
Total	80		10	15	8	10	13	10	14

they stopped smoking. The average number of cigarettes smoked was twenty-six daily, the range being from ten to forty-five. Only three patients smoked less than one pack daily.

In fifteen cases the improvement was due solely to stopping smoking. In ten cases bronchodilators, antibiotics, allergen injections and other therapy which had provided inadequate relief were continued. Impressive additional relief was observed when they stopped smoking.

The increase in ventilatory capacity was striking at times. Four bedfast orthopneic, emphysematous patients could walk around the ward comfortably in a few days after they stopped smoking. In ten cases the vital capacities were recorded before and several weeks after they had stopped smoking. The "first puff" into the vital capacity machine, a rough measure of usable tidal air, increased 20 to 33 per cent in the four cases in which it was observed. The total vital capacity increased 9 to 31 per cent in nine, and remained the same in the tenth case.

Eighteen of the twenty-five cases no longer wanted to smoke. The craving was mild and occasional in five others. In two it was still strong several months after they had stopped. Fifteen continued to cough or wheeze when exposed to smoke-filled rooms.

Improvement in the other symptoms, in Table II, was only slightly less impressive than in the respiratory complaints.

DISCUSSION

The recent literature on the effects of smoking is enormous. Gsell,⁸ Mibashan,⁶ Scott,¹⁰ and Woodward¹⁴ have interesting surveys of the smoking problem. In the literature on smoking and respiratory diseases, the trend has been to compare the incidence of respiratory syndromes in

SMOKING—SWINEFORD AND OCHOTA

smokers and non-smokers.^{1,2,4,7,8,11,13} Very little has been written to illustrate the benefits which might accrue to victims of chronic respiratory disorders as a reward for abstinence from smoking. Waldbott¹² reported improvement in an asthma-like syndrome. Phillips et al.⁹ reported striking improvement in cough in fifty-six of fifty-eight men. Lowell et al.⁵ suggested that emphysema might be due to smoking but did not comment on benefits from not smoking.

It is not always easy to persuade patients to stop smoking. The economic aspects, especially medical care costs; the progressive debility of most chronic lung diseases; the futility of trying to ignore the usually obvious role of smoking; the impossibility of determining the role of smoking, in the individual syndrome, while still smoking; the necessity for complete abstinence—are all stressed initially. In this clinic, all smokers with chronic respiratory symptoms are advised to stop. If they continue, and a detailed survey of the respiratory system fails to provide some other effective source of relief, the patients are told to seek medical advice elsewhere unless they stop smoking immediately. These cases represent a small percentage of the chronic respiratory problems seen in this clinic.

SUMMARY AND CONCLUSIONS

Forty-six patients who had chronic respiratory disorders improved after they stopped smoking. The records of twenty-five of these were analyzed for this report. Cough, dyspnea on exertion, asthma, frequent colds or perennial hay fever were recorded ninety-six times in twenty-five cases. Eleven had undiagnosed chest pain. Eighteen of these 107 symptoms disappeared completely. Forty-one were markedly (75 to 90 per cent) improved. Only thirteen of the 107 respiratory and fourteen of the eighty other symptoms did not improve.

In fifteen of the twenty-five patients, respiratory improvement was attributed solely to abstinence from smoking. It was thought to be a major factor in the other ten. The desire to smoke disappeared completely in eighteen of the twenty-five patients soon after the benefits became apparent. It persisted strongly in only two.

Six troublesome non-respiratory complaints were noted eighty times. Ten of these were relieved completely. Twenty-three improved markedly (75 to 90 per cent).

There are no established clinical criteria for the recognition of the role of smoking in the individual case, except abstinence. The mechanism by which smoking causes respiratory symptoms is not known. Non-specific irritation is probably more important than is a specific allergic reaction.

Patients with mild chronic respiratory symptoms should stop smoking as a prophylactic measure against severe symptoms and as a diagnostic

SMOKING—SWINEFORD AND OCHOTA

procedure. Patients with moderate to severe respiratory symptoms should stop smoking in the attempt to retard the progress of their disease and to enjoy the degree of relief which many will obtain.

Chronic respiratory disorders offer tangible material with which to study some of the untoward effects of smoking and the rewards of abstinence.

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Submitted August 15, 1957

ON SEPARATION OF MIND AND BODY

"One must put aside superstition, mythology, parallelism and other outworn creeds, and accept simply the fact that all stimuli which play on an organism are physical, that all phenomena which take place in organs are organic and that the psychologic processes although the most complex are not exceptions."—STANLEY COBB, M.D., *Archives of Internal Medicine*, 64:1328.

SEVERE ALLERGIC REACTION TO PIGNOLIA NUT

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and
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ACUTE ALLERGIC reactions to foods are not infrequent. The old saying "One man's meat is another man's poison" bears out this point. A severe reaction to a specific food can produce various manifestations associated with the allergic state. It may cause respiratory symptoms such as nasal swelling, blockage, and sneezing, or it may progress further and cause laryngeal edema with difficulty in swallowing and breathing or hoarseness. There might be chest tightness alone or a fully developed asthmatic episode. The reaction may consist of generalized urticaria and angioneurotic edema, with or without marked pruritus. Gastrointestinal disturbances, such as nausea, vomiting, abdominal cramps and diarrhea may be violent.

The case we are about to present was unusual because a few minutes after ingestion of a particular item of food, the patient developed most of the symptoms just outlined. Fortunately, the patient survived and later we were able to determine the cause of the reactions by direct testing on the patient and by passive transfer.

CASE PRESENTATION

The patient, a teacher, aged thirty-two, was in good health until March 11, 1956, when she ate a piece of candy called an "Irish Potato," which is usually sold only for St. Patrick's Day. About fifteen minutes later, she noticed roughness and scratchiness of the throat, followed by nausea, severe vomiting, abdominal cramps and diarrhea. Hives appeared over the chest, neck, hands, ankles, and feet, and generalized redness and blotching with marked pruritus covered her body. Her nose became stuffy and she felt she could neither inhale nor exhale. Fullness was felt in her throat; she could neither swallow nor speak clearly, and her voice was hoarse. Dizziness developed, and chills alternated with a generalized warm feeling. About thirty minutes after ingestion of the candy, the patient was in the Chicago Wesley Memorial Hospital emergency room with impending peripheral vascular collapse.

Examination revealed pallor of the face with cyanosis of the hands and feet, generalized blotching of the skin and giant hives. There were hyperactive bowel sounds and tenderness in the mid-epigastric area. The lungs were clear. The blood pressure was 90 systolic and 60 diastolic; her temperature was 99.2° F.

Epinephrine was given immediately, followed by intravenous ACTH and by 50 mgs Benadryl®. Relief was quick and satisfactory. Treatment included continuous intravenous drip consisting of thirty units of ACTH in 1000 cc of glucose in distilled water every eight hours for twenty-four hours. At the end of this interval, a switch was made to ACTH-gel, in decreasing dosages, so that by the time she left the hospital she was receiving no medication. While hospitalized she received Benadryl®, mgs 25, q.i.d., orally, and sodium amytal the first night for sedation. On discharge three days later, she had completely recovered.

Dr. Santos is an associate Fellow of The American College of Allergists.

REACTION TO PIGNOLIA NUT—SANTOS AND UNGER



Figs. 1, 2 and 3.

The hospital laboratory reports were as follows: Hematocrit, 42 per cent; urine negative; Kahn negative; white blood count, 15,950, of which 77 per cent were neutrophils, 15 per cent lymphocytes, 4 per cent monocytes, and 1 per cent eosinophils.

Review of her history revealed she had always been in good health. She had had atopic dermatitis at the age of one and again at three, with clearing each time after the family cat was removed from her home. She also had one prior episode of urticaria but the cause was not determined. For many seasons she suffered mild hay fever. There was no history of other allergy in the family and, as far as the patient knew, no evidence of drug or food idiosyncrasies.

Allergy Investigation.—We proceeded to analyze the specific cause of this severe allergic reaction. The firm that has manufactured "Irish Potatoes" for twenty years informed us that the ingredients are always the same: A core consisting of coconut, sugar and corn syrup, a coating of cinnamon, and a topping of four or five Pignolia nuts.

Eight days following the reaction, the patient received skin tests by the scratch method. These tests showed large reactions to members of the ragweed and fungi groups, and moderate reactions to June grass, oak, dog hair, castor bean, and Mayflies. Tests for foods revealed mild reactions to barley and yeast. No intradermal tests were given. Pignolia nuts were pulverized and scratch tests were done. The reaction was violent and almost immediate. There was marked erythema, formation of a large wheal with pseudopodia and marked itching. The control site was completely negative as can be seen in the first picture.

Since then we have done scratch tests with Pignolia nut extract on more than 150 patients, and have had only one moderately positive reaction.

About sixty days after the severe reaction noted in our patient, passive transfer studies were performed using two physicians as recipients, one about twice as old as the other (both individuals were known not to be allergic). Pignolia nut extracts in 1:100,000 and 1:10,000 dilutions were injected intradermally into sensitized sites. Results were striking, especially in the younger recipient, with large wheals and pseudopodia. The control sites were completely negative in response. This is illustrated in the second picture.

About forty-eight hours after the passive transfers were performed, each recipient ate eight or ten of the nuts. In approximately half an hour, in recipient Number 2 (the younger man), the sites where the patient's serum had been injected became swollen, erythematous, and itchy, especially those sites where the nut extract had been injected. Recipient Number 1 (the older man), had similar reactions but milder and more delayed. The third picture shows these positive reactions. The tests reveal that in doing passive transfer studies it is better to select a

REACTION TO PIGNOLIA NUT—SANTOS AND UNGER

young adult, if possible, as reactions are usually larger in this group as compared to those of older age.

From the above data, the diagnosis of allergy to Pignolia nuts was obvious, and strict avoidance was advised. Hyposensitization was unnecessary.

THE PIGNOLIA NUT

Pignolia nut is the trade name of the edible seed of the nut-pine tree. The tree is native to Italy, Spain and Turkey. The seeds are taken from the trees' cones after they are sun-dried and cracked open by hand.

Their composition is as follows:

Water	6%
Protein	33.9%
Fat	49%
Total carbohydrates	6.9%
Ash	3-4%
Food value per pound.....	2,845 calories or 178 calories per ounce

Yearly, about 200,000 pounds of these nuts are imported into the United States. Various national groups eat the nuts, mix them in sausages and cakes, or use them on various types of cookies. (Above data and information were obtained from the United States Department of Agriculture.)

SUMMARY

1. This is apparently the first case report of a severe allergic reaction following ingestion of one piece of candy containing pine nuts.
2. Direct skin tests (scratch) were strongly positive for this nut.
3. Passive transfer tests were also positive.
4. Pignolia nuts are eaten either alone or mixed in foods such as sausage, cakes, candy or cookies.

30 North Michigan Avenue, Chicago 2, Illinois (Santos)

185 North Wabash Avenue, Chicago 1, Illinois (Unger)

Submitted March 6, 1957

Resubmitted November 14, 1957

BOOKS IN THE PHYSICIAN'S LIFE

"Thus we see that the practicing physician must be guided by his daily *needs*, the research man by his *duty* to expand his research, and the teacher by his *desire* to enrich and improve his teaching. But to a certain degree all three, the practitioner, the research worker, and the medical teacher, should engage in all three categories of reading, devoting the greatest part of their time to what they *must* read, what time they have left over to what they *ought* to read, and any time they can steal to what they *want* to read."—F. MARTI-IBANEZ, M.D., *Books in the Physician's Life, Internat. Rec. Med.*, 168:10 (Oct.) 1955.

Editorial

The opinions expressed by the writers of editorials in the ANNALS do not necessarily represent the group opinion of the Board or of the College.

THE ALLERGIST AND POLIOMYELITIS VACCINE

The Surgeon General of the Public Health Service, Dr. Leroy E. Burney estimates that there are fifteen million children and at least thirty million adults below the age of forty who have not had any injections of anti-poliomyelitis vaccine. All the vaccine needed is available or can be manufactured as required. It is inexpensive and safe. It takes three injections given over a period of eight months. If we begin today, all of our patients can develop high immunity before the Spring of 1949.

Among physicians, allergists are most likely to see patients often, regularly and under circumstances which make it easy to tell the patient or his parents of the necessity for the three injections. For the allergist, the administration of the vaccine can be a routine procedure. Patients possibly sensitive to any ingredient of the vaccine are in the right hands when an allergist supervises their poliomyelitis vaccine program.

Any allergist's patient who becomes crippled with poliomyelitis will, all his life, suffer from both the disability of the sequelae of his disease and the knowledge that his allergist, by simple, painless means could possibly have averted the tragedy. For those patients taking injection treatment who cannot afford to pay for the vaccine, why not give it, anyway?

THE ALLERGIST AND ANNALS OF ALLERGY

Every so often, the Editor or a member of the Editorial Board is reproached for accepting for publication a paper which is not "practical" or which reports results in fields apparently far removed from those of every day allergy. What have iso-hemo-agglutinins or electrophoresis of antibody fractions or verbatim reports of psychiatric interviews to do with the injection treatment of ragweed hay fever? But these communications are related and part of the price allergists pay for having chosen a specialty basically inter-disciplinary in nature. The prefix "inter" is here given all of its connotations as "between," "among," "mutually," "reciprocally," and "together."

The expert in pulmonary function studies may not be deeply interested in the protein fractions of pollen and the expert in drug reactions may not be overly concerned with psychosomatic relationships but all can practice a high grade of allergy for the simple reason that allergists are specialists within a framework of what is truly a special type of specialty. In the

EDITORIAL

present state of our knowledge no one can know all of the field of allergy and few, if any, try to be expert in each of its subdivisions.

Despite the utmost lucidity of thinking and clarity of expression, there are limits beyond which a paper cannot go in being clear to every reader because the author is properly recording his results for the expert in the same field. There are parts of any paper clear to the widely read allergist, but he too, cannot be expert in every part of our subject.

But, the highly theoretical paper of yesterday concerned with a discussion as to the possible reason for the remission of asthma during pregnancy and jaundice leads to today's practical administration of the steroid hormones. Over and over again today's theory becomes tomorrow's practice.

In the pages of the *ANNALS* are printed those papers given at the annual meetings as accepted by three members of the Editorial Board and such papers as are submitted or solicited between scientific sessions. The *ANNALS* is limited to these, the annual reviews of progress in each aspect of our field, the editorials, and the notes of papers likely to be of interest to our Associate Fellows and Fellows.

With more papers submitted, shorter reviews written more concisely and more pages of text, we should be able to give our readers a wider variety of more interesting reading matter. We would please very few if we limited the function of the *ANNALS* to printing papers within the narrow limits of any special part of our field. The innovations which began with the January-February issue this year should result in pleasing more and more of our readers as issue follows issue. Perhaps some day there will be subdivisions of the *ANNALS* devoted to each aspect of allergy. Then we can please everybody.

ARE ALLERGIES PREVENTABLE?

Practical measures soon may be found to prevent allergic reactions in potentially allergic infants and children (those with a family history of allergy), predicts Dr. Rudolf L. Baer† of New York, if clinical studies substantiate preliminary findings in laboratory animals.

Experimental evidence in animals shows that exposure to an allergen during the first few days and perhaps weeks of life produces some degree of tolerance or immunity to that allergen—at least for a period of time.

Newborn rabbits infused with human plasma or bovine serum albumin, for example, became immunologically unresponsive to these antigens for at least eleven months.

The tolerance manifested itself in an inability or in a diminished capacity to become allergically sensitized to that particular allergenic agent. Dr. Baer emphasized, however, that thus far these phenomena have been demonstrated only for certain allergens in certain species of animals.

Another study indicates that certain manipulations in the diet of the pregnant mother of a potentially allergic infant may be helpful in preventing allergic reactions in the child.

†Baer, R. L.: Remarks on prevention of allergic sensitizations, *AMA Archives of Dermatology*, 77:682 (June) 1958.

Papers of Interest

- Cournand, A.: Pulmonary circulation (its control in man with some remarks on methodology). *Science*, 125:1231-1235 (June 21) 1957.
Not simple! Not easy!
- Callaway, J. Lamar: Dermatologic research: An office procedure? *J. Invest. Dermat.*, 27:215 (Oct.) 1956.
Lists which clinical observations of the associated laboratory studies resulted in important advances in medicine and those which were purely laboratory studies.
- Rappaport, Israel: The problem of the visceral function of the lungs. *Dis. of Chest*, 25:1 (Jan.) 1954.
The author advances for the second time his concept of intrinsic lung function, visceral in nature and nonmechanistic. He points up the unsolved problems of lung function and disfunction.
- Lake, Clifford F., Logan, George G., and Peters, Gustavus A.: Treatment of ragweed hay fever with powdered hydrocortisone applied intranasally. *Proc. Staff. Meet. Mayo Clin.*, 32:22 (Oct. 30) 1957.
Fifteen adults and three children were treated by intranasal insufflation of hydrocortisone powder when symptoms had not been controlled by conventional treatment. A daily dose of 15 mg of hydrocortisone, divided into three doses was adequate. Irritation or exacerbation occurred in one patient.
- Feinerman, Burton and Harris, Lloyd E.: Unusual interstitial pneumonitis. *Proc. Staff. Meet. Mayo Clin.*, 32:22 (Oct. 30) 1957.
Case reports of two rare disorders: one patient responded to steroid hormones; the second, a seven-month-old girl, did not respond and died after fourteen days of treatment, following admission to the hospital.
- Bridges, Robert A. et al.: Death due to novobiocin sensitivity. *J. Pediat.*, 50:579-585, 1957.
This occurred in a fourteen-year-old boy who received 2 gm of novobiocin twice daily for eight days. Postmortem examination revealed acute diffuse hepatic necrosis and generalized lymphoid hyperplasia.
- Bibliography on virus hepatitis, 1954-56. *Bull. World Health Organ.*, 17:163-79 (No. 1) 1957.
More than 350 references to a subject of major importance to physicians who give injection therapy.
- Moyes, E. N. and Kershaw, R. A.: Long-continued treatment with tetracycline and prednisolone in chronic bronchitis. *Lancet*, 2:1187 (Dec. 14) 1957.
Metisteroids of little help.
- Wunderly, Ch.: Immunelectrophoresis in agar-gel. *Experientia*, 13:421 (Nov. 15) 1957.
Present-day techniques with results of studies of reactions of antigens and antibodies in gels.
- Cepellini, R., Polli, E. and Celada, F.: A DNA-reacting factor in a serum of a patient with lupus erythematosus diffusus. *Proc. Soc. Exp. Biol. & Med.*, 96:572, 1957.
- Robbins, W. C., Holman, H. R., Deicher, H. and Kundel, H. G.: Complement fixation with cell nuclei and DNA in lupus erythematosus. *Proc. Soc. Exp. Biol. & Med.*, 96:575, 1957.
These two papers, together with two others recently published in Europe, provide evidence, that the sera of patients suffering from lupus erythematosus produce complement fixing antibodies reactive with cell nuclei. They support the hypothesis that in lupus erythematosus there is an antigen-antibody reaction.—A.J.W.
- Lewis, G. W.: Acute immediate reactions to penicillin. *Brit. M.J.*, 1:1153 (May 18) 1957.
In four of twelve patients, reactions to penicillin were caused by rapid intravascular injection of procaine suspensions, and in five, by accidental intravascular injection or back-seepage. In two others, who were sensitized; and in one, reaction came after an injection of a known toxic, penethamate hydriodide. A plan for minimizing the incidence and severity of reactions is given.
- Leslie, A., and Simmons, D. H.: Evaluation of the bronchodilator, caytine. *Am. J. Med. Sci.*, 234:321 (Sept.) 1957.
The authors conclude, from inhalation studies in thirty-two patients, that "caytine has clinical value . . . enough to warrant its inclusion in the armamentarium of bronchodilator aerosols."

PAPERS OF INTEREST

- Dekker, E., Pelser, H. E., and Groen, J.: Conditioning as a cause of asthmatic attacks. *J. Psychosom. Research*, 2:97-108, 1957.
The authors describe two asthmatic patients whose reactions to inhalation studies gave the impression that the patients had become conditioned to the inhalation situation and to "fragments" of the situation.
- Min-Hua, Liu, Ching-Ming, Kao, and Ping-Hsing, Wei: Occurrence of mites in bronchiectasis sputum. *Chinese M.J.*, 75:578-584, January, 1957.
The occurrence of mites in the sputum of a bronchiectasis case is reported. Lack of eosinophilia suggested that mites may not be significant in tropical eosinophilia. Arsenicals were found of little value in treatment of mite infestation of the lung.
- Patton, John D.: The doctor-patient relationship. *North Carolina Med. J.*, 18:279-282 (July) 1957.
If the physician fulfills his expected role, he will be practicing the art of medicine, or psychotherapy, regardless of the type of patient he is treating or the type of treatment he is rendering.
- Barrock, James J.: Cold wave dermatitis. *Clin. Med.*, October, 1957.
Contact dermatitis may occur in a few patients; severe sensitivity may develop after repeated exposure.
- Rubenstein, M. W.: Psychocutaneous disorders. *Clin. Med.*, 1243, October, 1957.
Though apparently the patient's disorder is or seems limited to the skin the total organism may be involved in a series of sociologic, psychologic, and emotional crises.
- Epstein, J. H., Brunsting, L. A., Petersen, M. C., and Schwarz, B. E.: A study of photosensitivity occurring with chlorpromazine therapy. *J. Invest. Dermat.*, 28:329 (May) 1957.
Nine of seventy-two patients exposed to ultraviolet rays while taking chlorpromazine developed exaggerated sunburn reactions.
- Scott, O. L. S.: Advances in the treatment of skin diseases. *Practitioner*, 179:387 (Oct.) 1957.
Review of treatment with corticosteroids, chloroquine, tranquillizing and antibiotic agents, sulphones, sulphonamides, and physical agents.
- Weil, M. H., and Spink, W. W.: A comparison of shock due to endotoxin with anaphylactic shock. *J. Lab. Clin. Med.*, 50:501 (Oct.) 1957.
The injection of endotoxin causes a reaction so similar to anaphylactic shock that a common mechanism is postulated.
- Germuth, F. G., Jr., Flanagan, C., and Montenegro, M. R.: The relationships between the chemical nature of the antigen, antigen dosage, rate of antibody synthesis and the occurrence of arteritis and glomerulonephritis in experimental hypersensitivity. *Bull. Johns Hopkins Hosp.*, 101:149 (Sept.) 1957.
The minimum dose of bovine gamma globulin causing allergic lesions in the rabbit was 0.5 gm; of bovine albumin, 0.25.
- Saito, S., Hosoya, T., and Tomizawa, K.: Serotonin in surgery. *Gunma J. Med. Sci.*, 6:14 (Mar.) 1957.
In surgical stress and anaphylactic shock, elevation of the serum serotonin was observed in mesenteric as compared to hepatic venous blood.
- Hsiao-Tseng, Chou, and Chen-Yeh, Chu: Idiopathic thrombocytopenic purpura. *Chinese M.J.*, 75:678-681 (August) 1957.
Splenectomy is the treatment of choice in chronic recurrent purpura, according to the authors who based their conclusions on a study of fourteen cases. Further observation is required concerning the treatment of this disease in the acute form.
- Chakravarti, Amal: Malignant tumours of lung. *Calcutta M.J.*, 54:245 (July) 1957.
Observations of fifteen variously presented cases showing frequency of initial symptoms occurring in this order: (1) fever with cough, (2) fever, (3) difficulty in breathing, (4) chest pain, (5) fever and chest pain, (6) hoarse voice, (7) weight loss and presenting symptoms in order of frequency were: (1) haemoptysis, (2) pain, (3) chest pain and fever, (4) fever, (5) hoarseness, (6) weight loss, (7) dyspnea, (8) cough and fever, and (9) cough with chest pain.
- Markiewitz, K. H.: On the isolation and purification of the allergenically active alkenyl phenols of poison ivy and related plants. *Dissertation Abst.*, 17:19 (Sept.) 1957.
Describes the synthesis of toxic components.
- Dowling, H. F., Jackson, G. G., and Inouye, T.: Transmission of the experimental common cold in volunteers. II. The effect of certain host factors upon susceptibility. *J. Lab. Clin. Med.*, 50:516 (Oct.) 1957.
Susceptibility is higher in subjects with a positive history of allergy. No relationship discovered to tobacco smoking and tonsillectomy.

PAPERS OF INTEREST

- Fred, Ezekiel: Pulmonary changes following exposure to commercial acetylene fumes. (Case report and roentgen films.) Kaiser Foundation Med. Bul., 5:341-344 (Sept.-Oct.) 1957.
Eighteen hours before admission, the patient had inhaled acetylene gas from a leaking torch. Rhonchi and wheezes were present. The chest film showed pulmonary edema, multiple areas of bronchopneumonia, and pleural effusion.
- Mainland, Donald: Safety in numbers. Circulation, 16:784-790 (Nov.) 1957.
Interesting discussion of statistics in clinical studies.
- Najjar, V. A., Sidbury, J. B., Jr., and Fisher, J.: Further studies on the mechanism of antibody-antigen interaction. Biochem. Biophys. Acta, 26:114 (Oct.) 1957.
Known to Fellows from 1957 Post-Graduate course and in updated form in Atlantic City, April, 1958.
- Morrison, B., Bass, D., Davis, J. A., Hobson, D., Madsen, T. I., and Masters, P. L.: Acute lower-respiratory infections in childhood. Lancet, 2:1077 (Nov. 30) 1957.
Chemotherapy is necessary because of dangers of secondary bacterial invasion.
- Miller, C. A.: Problems associated with routine immunizations. Postgrad. Med., 22:445 (Nov.) 1957.
Review of modern immunization procedures in diphtheria, whooping cough, smallpox, poliomyelitis and tetanus.
- Dworetzky, Murray: Allergic diseases of the eye. New York State J. Med., 57:4 (Feb.) 1957.
Good review.
- Edwards, G., Buckley, A. R., Fear, E. C., *et al.*: Adult chronic bronchitis—the infective factor and its treatment. Brit. M. J., 2:259-264 (Aug. 3) 1957 (London)
Toxic effects were not a serious problem of treatment with 0.5 gm or less oxytetracycline and/or a sulfonamide. Improvement of fifty-three patients was thirty-seven per cent and the autogenous hemophilus influenzae vaccine had little, if any, clinical effect.
- Silvette, H., Larson, P. S., and Haag, H. B. (From the Dept. of Pharmacology, Medical College of Virginia, Richmond, Virginia): Immunological aspects of tobacco and smoking.
Excellent review. Well documented.
- Mathiesen, E. O., and Trolle-Lassen, C.: Renal elimination of penicillin by the aged. Scand. J. Clin. Lab. Invest., 9:213 (No. 3) 1957.
The renal clearance rate of benzyl penicillin decreases with age.
- Costello, M. J., Jaimovich, L., and Dannenberg, M.: Treatment of pemphigus with corticosteroids. J.A.M.A., 165:1249 (Nov. 9) 1957.
Mortality rate lowered by steroid administration.
- Munoz, J.: Production in mice of large volumes of ascites fluid containing antibodies. Proc. Soc. Exp. Biol. Med., 95:757 (Aug.-Sept.) 1957.
Intraperitoneal injection of either egg albumin or bovine serum albumin mixed in Freund's adjuvant leads to the accumulation of large amounts of peritoneal fluid containing antibodies to the antigen used in approximately fifty per cent of mice so treated.
- Ortega, L. G., and Mellors, R. C.: Cellular sites of formation of gamma globulin. J. Exper. Med., 106:627 (Nov. 1) 1957.
Gamma globulin (as is antibody) originates in germinal and plasma cells.
- Zeligman, I., and Hubener, L. F.: Experimental production of acne by progesterone. A.M.A. Arch. Dermatol., 76:652 (Nov.) 1957.
In ten of eleven subjects given progesterone, acne vulgaris developed which decreased six weeks after administration ceased.
- Bell, J. A., Ward, T. G., Kapikian, A. Z., Shelokov, A., Reichelderfer, T. E., and Huebner, R. J.: Artificially induced Asian influenza in vaccinated and unvaccinated volunteers. J.A.M.A., 165:1366 (Nov. 16) 1957.
Approximately 75 per cent of unvaccinated and fifty per cent of vaccinated subjects responded with symptoms to exposure of Asian influenza virus.
- Karrel, I. A.: Thrombocytopenic purpura due to an oral diuretic (mictine). Canad. Med. Assoc. J., 77:959 (Nov. 15) 1957
Not previously reported.

In Memoriam

HAL McCLUNY DAVISON, M.D.

Dr. Hal McCluny Davison began to have symptoms of Hodgkin's Disease during May, 1957. This caused him no real concern until December, 1957, when he was hospitalized and received transfusions. His illness became complicated by a ruptured diverticulum with resulting peritonitis. His condition was so acute that surgery was done as a life-saving measure on April 13. He survived this operation well and seemed better for several days but gradually grew worse and died on April 26, 1958. He was buried in West View Cemetery in Atlanta, Georgia.

Hal McCluny Davison was born in Woodville, Georgia on October 2, 1891, being one of four children, he had two brothers and a sister who died many years ago. His oldest brother was a prominent Baptist Minister, Dr. Charles C. Davison. His other brother, Dr. Thomas C. Davison, was a well-known and outstanding surgeon.

Doctor Hal received the Bachelor of Arts and Bachelor of Pharmacy degrees at Mercer University, Macon, Georgia. During his College years he received his numeral "M" in football at Mercer. He received his M.D. degree in 1915 from the Atlanta Medical College (now Emory University). Post-graduate work in internal medicine was carried out at New York Post-Graduate Hospital in 1921 and special training in immunology at Cornell University in 1923.

He was in the United States Army Medical Corps during World War I, stationed in Siberia. He received his discharge there at the end of the war and became affiliated with the American Red Cross in Siberia. While there he met and married the former Natasha Beklemisheva, who survives him. They have two sons the oldest of whom is Captain Peter H. Davison of the United States Air Force now stationed in Berlin, Germany. Peter has three children. His second son is Dr. Alexis H. Davison who has two children. Doctor Alexis is now serving his first year residency at the University of Virginia Hospital in Charlottesville, Virginia.

Hal Davison had broad interests not only in medical affairs, but also in civic and educational circles. He was a trustee of Mercer University and over a period of years was honored as president of the following organizations: General Securities Corporation, Atlanta, Georgia; General Life Insurance Company, Atlanta, Georgia; Active Voters, Atlanta, Georgia; International Conference of Christians and Jews, Atlanta Chapter, and he was a member of a number of local social and professional groups. He held many important positions on various committees dealing with international problems in the field of medicine.

Hal McCluny Davison was a Fellow of The American College of Allergists, having served in this organization in the capacity of president, member of the Board of Regents, and chairman of the Board of Directors. Further, he served on the Editorial Board of the *ANNALS OF ALLERGY*. He was a Fellow of the International Association of Allergists, having been one of the original Founders Group. He was a Fellow of The American Academy of Allergy and of the American College of Physicians. He was a member of the Southern Medical Association, the American Therapeutic Society, the American Academy of Applied Nutrition, the American Heart Association, the Medical Association of Georgia, and a member of the International Academy of Medicine. He was past president of the Southeastern Allergy Association, The Medical Association of Georgia 1956-1957, The Fulton County Medical Society and of the Fifth District Medical Society. He served as

IN MEMORIAM

Chief of Medicine at the Atlanta Baptist Hospital from 1943 until he resigned this post on June 30, 1956.

Doctor Hal was in great demand as a speaker for many medical groups all over the United States. In 1955, he addressed the International Congress of Allergy at its Meeting in Zurich, Switzerland.

Hal McCluny Davison has made many contributions to the subject of allergy—particularly in the area of food allergy, and he was an untiring clinician and investigator. His opinions on all subjects relating to allergy as well as internal medicine were greatly respected—not only by his local associates, but also by those taking responsibility on a national level. Dr. Davison always showed a keen interest and was never too busy to lend inspiration to a young man in medicine towards greater fields of endeavor. Over a period of years he participated as an instructor in the postgraduate educational courses as put on by The American College of Allergists throughout the United States in various localities.

At medical meetings in his various capacities serving the many varied organizations, everyone looked forward always to seeing Hal Davison. This friendship extended to a large circle of physicians and their wives.

Dr. Davison was responsible for a number of men going into the specialty of allergy and carrying on this specialty at a high level—employing not only allergy, but the combination of allergy and internal medicine.

All personal relationship with Hal McCluny Davison was stimulating and he was a man of keen interest. He was original, practical and scientific in his approach to all new problems. Under pressure he was efficient, ingenious and resourceful—a leader and an inspiration to all who worked with him. He will be sorely missed not only by his family, but also by a wide circle of personal friends and clinicians.

His name will long be remembered as one of the leading American men of science and allergy.

J.W.T.

EDWIN A. GRIFFIN

Dr. Edwin A. Griffin of Brooklyn, New York, died on December 29, 1957, at the age of seventy.

Dr. Griffin graduated from New York University in 1909. He was senior otolaryngologist at the Samaritan Hospital, and senior surgeon at the Brooklyn Eye and Ear Hospital. He was a Diplomate of the American Board of Otolaryngology, a Fellow of both the American and International Colleges of Surgeons, and a member of The American Academy of Ophthalmology and Otolaryngology, and the American Laryngological, Rhinological, and Otological Society.

He was past president of the Pan-American Medical Society, and served as chairman of the Publications Committee of the Medical Society of the County of Kings, New York, for eight years. He was second vice-president of the County Society for three years, and was a delegate of the Medical Society of the State of New York for four years, as well as a former Board of Trustees member.

Dr. Griffin was elected to Fellowship in The American College of Allergists in 1944.

JOHN A. HURLBUT

Dr. John A. Hurlbut, Madison, Wisconsin, passed away on December 23, 1957. He is survived by a son, Jack, and one sister, Mrs. Hazel Benbrook of Chicago.

Dr. Hurlbut graduated from Northwestern University Medical School in 1924, and interned at Methodist Hospital, joining its staff in 1925.

He was a member of the Dane County Medical Society and the Wisconsin State Medical Society. He was elected to Fellowship in The American College of Allergists in 1944.

News Items

THE AMERICAN COLLEGE OF PHYSICIANS

The American College of Physicians has scheduled future meetings as follows:

In 1959: Chicago, Illinois, April 20-24. Headquarters, the Conrad Hilton Hotel. Chairman is Dr. Eliot E. Foltz, 530 Winnetka Avenue, Winnetka, Illinois.

In 1960: San Francisco, California, April 4-8. Headquarters to be selected. Chairman is Dr. Robert F. Escamilla, 384 Post Street, San Francisco, California.

In 1961: Bal Harbour, Florida, May 8-12. Headquarters, the Americana. Chairman to be selected.

FLORIDA ALLERGY SOCIETY

The Florida Allergy Society elected the following officers at their meeting held May 11, 1958:

President.....	G. Fredrick Hieber, M.D.
Vice President and President-elect.....	James H. Putnam, M.D.
Secretary-Treasurer.....	I. Irving Weintraub, M.D.

MICHIGAN ALLERGY SOCIETY

The Michigan Allergy Society recently elected their officers for the coming year, as follows:

President.....	Bernard Dickstein, M.D.
Vice President.....	Milton J. Steinhardt, M.D.
Secretary-Treasurer.....	Robert G. Lovell, M.D.

Those appointed to the Executive Committee were:

Bernard Dickstein, M.D.	S. Oskar Schreiber, M.D.
Sidney Friedlaender, M.D.	Milton J. Steinhardt, M.D.
Homer Howes, M.D.	Robert G. Lovell, M.D.

EDITOR WINS FIRST PRIZE IN ESSAY CONTEST

Doctor Ethan Allan Brown has been named the winner of the 1958 Mississippi Valley Essay Contest. He will present his essay at the annual meeting of the Mississippi Valley Medical Society to be held in Chicago, at the Hotel Morrison, September 24, 25 and 26, 1958. The essay entitled "A Program For The Treatment of Subacute Bronchial Asthma" will be published in the January, 1959, issue of *Mississippi Valley Medical Journal*.

MID-WEST FORUM ON ALLERGY

The Mid-West Forum on Allergy will hold its annual meeting on December 6 and 7, 1958, at the Sheraton-Cadillac Hotel, Detroit, Michigan. This meeting of the Forum is sponsored by the Michigan Allergy Society. For further information please write to John M. Sheldon, M.D., General Chairman, in care of the University Hospital, Ann Arbor, Michigan.

BOOK REVIEWS

ALLERGY IN PEDIATRIC PRACTICE. By William B. Sherman, M.D., and Walter R. Kessler, M.D., Ph.D. 296 pages. St. Louis: The C. V. Mosby Company, 1957. Price \$9.25.

Offering help to pediatricians who do not have extensive training in allergy, and intended as a "simple and practical" survey of the field, this book has an easy style and good organization to commend it. Unfortunately in its attempt at simplification, it has neglected to mention aspects of allergy that are quite significant in an introduction to the field.

The term "atopy" is a much used word in the book, despite admission by the authors that the term has been subject to a good deal of criticism—they admit that the influence of heredity has been questioned frequently and often is not established. The term, originally conceived in 1923 by Coca and Cooke, was supposed to refer to a specific illness manifested solely by human beings in which the immediate whealing reactions to skin tests with antigen and Prausnitz-Kustner reaction of passive transfer were demonstrable. Since that time, similar allergic conditions as seen in man have been noted in horses, dogs, cats and other animals. Eventually, Dr. Coca himself was obliged to abandon the tie between positive skin sensitizing antibodies and heredity when Rackemann demonstrated such antibodies in any human being infested with *Ascaris*.

The chapter, "Drugs Used in the Treatment of Allergy," is found of particular value to the practicing physician. The indications for the use of these drugs are carefully noted, and the abuses resulting from misuse or overdosage are clearly outlined.

In the chapter, "Anaphylaxis in Pediatric Practice," mention is made of Loeffler, who in 1932 reported on the occurrence of febrile transitory infiltrations of the lung associated with eosinophilia—findings noted essentially in cases with pulmonary tuberculosis. The writers neglect to point out that before this, in 1927, Peshkin described a condition seen in asthmatic children which he labeled "subacute pulmonary infiltration." The lesion in this condition could be either unilateral or bilateral and was commonly located at the cardiophrenic angles. The children were not even subacutely ill. Without any particular medication, the infiltration required from four to eight weeks to clear. This is a migratory type of inflammation not in any way associated with pneumonia or tuberculous infection.

In the chapter on "Diagnosis of the Specific Causative Allergens," there is a discussion (p. 124) of the significance of skin tests. Under the sub-heading, "Inhaled Antigens," where mention is made of the testing of eczematous children who have never had hay fever, the authors state that it is not unusual to find direct skin reactions or passive transfer reactions to ragweed pollen extract. They further write: "In the course of a few years, a considerable proportion of children showing such reactions may be expected to develop clinical hay fever." In view of this admission, it is surprising that the authors permit so large a number of children to go into active pollenosis when it is conceivably possible to institute successful preventive pollen therapy. Such prophylactic therapy has been advocated and practiced by many allergists. For many years, a positive skin reaction to an allergen has been regarded as a true immunological phenomenon. However, the statement is made by the authors that a positive reaction to pollens without clinical symptoms is nevertheless termed a "false positive" reaction (p. 125), despite their acknowledgment that such patients frequently develop active pollen allergy.

BOOK REVIEWS

The chapter on Allergic Rhinitis is clearly presented in orderly fashion and is thorough in its treatment.

In the chapter, "Bronchial Asthma" (p. 167), the authors in their strenuous attempt to define the meaning of sibilant and sonorous roles in infants and young children with or without fever have confused the terms "bronchitis," "asthmatic bronchitis," and "bronchial asthma." It becomes extremely difficult from their description to determine when "bronchitis" started and "asthmatic bronchitis" or "bronchial asthma" ends. The effectiveness of any drug including epinephrine hydrochloride in clearing up these conditions is to be obviously regarded as a fallacious differential diagnostic technique. In the light of these manifest differences, it is clearly evident that there is a great need for clarification of the term "bronchial asthma" itself.

Again in the chapter on "Diagnosis of the Specific Causation Allergens," the statement is made that "the reaction in the passively sensitized skin is strictly specific so that the results obtained by direct testing and passive transfer are essentially identical." This statement without the blessing of controversy is at complete variance with the facts—Peshkin and Fineman, in 1929, demonstrated that "the employment of, this procedure in a routine manner for the determination of the etiologic or the potential factors of allergy is unreliable and its application as a substitute for the 'direct method scratch and intradermal' of skin testing is impractical." Subsequently their findings were essentially confirmed by Chobot and Horowitz. However, the local passive transfer test is an important academic contribution to the science of allergy.

In the chapter, "Infection Treatment" (p. 136), the authors write, "Titration of the degree of sensitivity by intracutaneous tests with various dilutions of the antigen gives valuable information as to a safe initial dose." It is admitted that the practice and principles of serial dilution tests are now empirically taught and accepted by an impressive number of physicians as scientifically established facts. But Cooke and VanderVeer in 1927 stated that the serial dilution method of skin tests of patients with pollenosis is 50 per cent reliable as a guide to an optimum protection dose in the treatment. The problem of standardization of treatment with the aid of titration dilution tests still remains unresolved. There is no accurate or reliable means of gauging in advance the optimum dose of pollen or other antigen necessary to protect the patient. The optimum protection dose of pollen is determined rather by the actual experience gained with the use of pollen in the patient. In the final analysis, there is no assurance that serial titration tests can be relied upon "as to a safe initial dose" of antigen. To be wholly practical, the titration test should be entirely eliminated because it is simpler and less time consuming to inject the antigenic extract and commence the treatment with the safest possible solution which may be represented, for example, by a solution of pollen containing 1 Freeman-Noon pollen unit (1-1,000,000 or 0.00001 mg N. or 0.6 Protein Nitrogen units). From here on, it is only a matter of several injections in the treatment schedule to determine a patient's tolerance and at the same time treatment is being administered.

The chapter on infantile eczema is adequately covered and well done.

Perhaps for purposes of clarification or emphasis, some of the material was repeated a number of times throughout the text. The authors have made an honest attempt to present an abbreviated approach to the diagnosis and management of allergic disorders in children. Unfortunately, in trying to make it "simple and practical" they have ignored or glossed over issues that are basic in a sound orientation to the complex subject of allergy. However, for those physicians who wish to manage children's allergic syndromes within the framework of one school of thought, this book should meet their requirements.—H.G.R.

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Ayerst Laboratories (Theruhistin®)	A-14, A-15
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Brewer & Co., Inc. (Luasmin)	A-40
(Sus-Phrine)	A-22
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(Perazil®)	A-12
Center Laboratories, Inc. (Diagnostic and Therapeutic Allergens)	A-36
Classified Advertising	A-50
Coca-Cola	A-50
Dalare Associates (Rhu-Sem®)	A-46
Dome Chemicals, Inc. (Hist-A-Cort E)	A-18
Endo Laboratories, Inc. (Allergenic Extracts)	A-46
Fleet, C. B., Co., Inc. (Clysmathane®)	A-34
Greer Drug & Chemical Corp. (Allergenic Materials)	A-52
Grocery Store Products (Cream of Rice)	A-17
Hollister-Stier Laboratories (Desensitization for Insect Sting)	A-45
Irwin-Neisler & Co. (Dainite®-KI)	A-3
Jackson-Mitchell Pharmaceuticals, Inc. (Meyenberg Goat Milk)	A-41
Johnson & Johnson (Medicated Powder)	A-35
Knoll Pharmaceutical Co. (Quadrinal)	A-48
Lederle Laboratories Division (Aristocort®)	A-43
Leeming, Thos., & Co., Inc. (Nephenalin®)	A-33
Lilly, Eli, & Co. (Co-Pyroneil)	A-32
Luden Laboratories (Therapeutic Allergenic Extracts)	A-54
Luzier's (Cosmetics and Perfumes)	A-16
McNeil Laboratories, Inc. (Clistin®)	A-21, A-25
New York University Post- Graduate Medical School (Dermatology and Syphilology for the Pediatrician)	A-53
Organon, Inc. (Cortrophin®-Zinc)	A-47
Parke, Davis & Co. (Benadryl®)	A-7
Pfizer Laboratories (Neo-Magnacort®)	A-49
Puriton (Air Filter)	A-37
Riker (Medihaler-Epi® and Medihaler- Iso®)	A-55
Robins, A. H., Co., Inc. (Dimetane®)	A-51
Schering Corporation (Chlor-Trimeton® Syrup)	A-29
(Meti-Derm® Aerosol)	A-1
(Metreton®)	A-23
Sharp & Sharp (Dry Pollens and Powdered Allergens)	A-52
Sherman Laboratories (Elixophyllin)	A-8, A-9
Smith, Kline & French Laboratories (Teldrin Spansule)	Cover IV
Squibb (Kenacort)	A-6
(Florinef-S)	A-39
Stemen Laboratories, Inc. (Pollens and Powdered Allergens)	A-48
Tafel Sales Co. (Aerosol Pump)	A-53
Texas Pharmacal Co. (Allercreme®—Hypo-allergenic Cosmetics)	A-44
Thomas, Charles C (Medical Books)	A-24
Upjohn	Insert facing A-16
Wallace Laboratories (Miltown®)	A-13
Warner-Chilcott Laboratories Division (Tedral® Anti-H)	Cover II
Westwood Pharmaceuticals (Lowila® Cake)	A-42
Wyeth (Phenergan®)	A-19